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- (74) Agents: **HOGAN, John, W., Jr.**; American Home Products Corporation, Patent Law Dept., Five Giralda Farms, Madison, NJ 07940 et al. (US).
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- (71) Applicant: **AMERICAN HOME PRODUCTS CORPORATION** [US/US]; Five Giralda Farms, Madison, NJ 07940 (US).
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- (72) Inventors: **NELSON, Frances, C.**; 694 Terrace Heights, Wyckoff, NJ 07481 (US). **ZASK, Arie**; 21 East 90th Street, New York, NY 10128 (US). **CHEN, James, M.**; 4015 Marblehead Drive, San Ramon, CA 94583 (US). **MOBILIO, Dominick**; 35 Sneider Road, Warren, NJ 07059 (US). **NILAKANTAN, Ramaswamy**; 95 Birch Street, Closter, NJ 07624 (US).

(54) Title: **ORTHO-SULFONAMIDO ARYL HYDROXAMIC ACIDS, PROCESS FOR THEIR PREPARATION AND THEIR USE AS MATRIX METALLOPROTEINASE INHIBITORS**

(57) Abstract: Ortho-sulfonamido aryl hydroxamic acids are provided which are useful, inter alia, for the inhibition of matrix metalloproteinases and the treatment of conditions associated with overexpression of MMPs.

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ORTHO-SULFONAMIDO ARYL HYDROXAMIC ACIDS, PROCESS FOR THEIR PREPARATION AND THEIR USE AS MATRIX METALLOPROTEINASE INHIBITORS

5

10 Background of the Invention

The present invention relates to novel, low molecular weight, non-peptide inhibitors of matrix metalloproteinases (e.g. gelatinases, stromelysins and collagenases) which are useful for the treatment of diseases in which these enzymes are implicated such as arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system and HIV infection.

More particularly this invention provides orthosulfonamido aryl hydroxamine acids as matrix metalloproteinase inhibitors processes for their preparation and pharmaceutical compositions containing them.

Matrix metalloproteinases (MMPs) are a group of enzymes that have been implicated in the pathological destruction of connective tissue and basement membranes [Woessner, J.F., Jr. *FASEB J.* 1991, 5, 2145; Birkedal-Hansen, H.; Moore, W.G.I.; Bodden, M.K.; Windsor, L.J.; Birkedal-Hansen, B.; DeCarlo, A.; Engler, J.A. *Crit. Rev. Oral Biol. Med.* 1993, 4, 197; Cawston, T.E. *Pharmacol. Ther.* 1996, 70, 163; Powell, W.C.; Matrisian, L.M. *Cur. Top. Microbiol. and Immunol.* 1996, 213, 1]. These zinc containing endopeptidases consist of several subsets of enzymes including collagenases, stromelysins and gelatinases. Of these classes, the gelatinases have been shown to be the MMPs most intimately involved with the growth and spread of tumors, while the collagenases have been associated with the pathogenesis of osteoarthritis [Howell, D.S.; Pelletier, J.-P. In *Arthritis and Allied Conditions*; McCarthy, D.J.; Koopman, W.J., Eds.; Lea and Febiger: Philadelphia, 1993; 12th Edition Vol. 2, pp. 1723; Dean, D.D. *Sem. Arthritis Rheum.* 1991, 20, 2; Crawford, H.C; Matrisian, L.M. *Invasion Metast.* 1994-95, 14, 234; Ray, J.M.; Stetler-Stevenson, W.G. *Exp. Opin. Invest. Drugs*, 1996, 5, 323].

It is known that the level of expression of gelatinase is elevated in malignancies, and that gelatinase can degrade the basement membrane which may

lead to tumor metastasis [Powell, W.C.; Matrisian, L.M. *Cur. Top. Microbiol. and Immunol.* 1996, 213, 1; Crawford, H.C; Matrisian, L.M. *Invasion Metast.* 1994-95, 14, 234; Ray, J.M.; Stetler-Stevenson, W.G. *Exp. Opin. Invest. Drugs*, 1996, 5, 323; Himelstein, B.P.; Canete-Soler, R.; Bernhard, E.J.; Dilks, D.W.; Muschel, R.J.

5 *Invasion Metast.* 1994-95, 14, 246; Nuovo, G.J.; MacConnell, P.B.; Simsir, A.; Valea, F.; French, D.L. *Cancer Res.* 1995, 55, 267-275; Walther, M.M.; Levy, A.; Hurley, K.; Venzon, D.; Linehen, W.M.; Stetler-Stevenson, W. *J. Urol.* 1995, 153 (Suppl. 4), 403A; Tokuraku, M; Sato, H.; Murakami, S.; Okada, Y.; Watanabe, Y.; Seiki, M. *Int. J. Cancer*, 1995, 64, 355; Himelstein, B.; Hua, J.; Bernhard, E.;

10 Muschel, R.J. *Proc. Am. Assoc. Cancer Res. Ann. Meet.* 1996, 37, 632; Ueda, Y.; Imai, K.; Tsuchiya, H.; Fujimoto, N.; Nakanishi, I.; Katsuda, S.; Seiki, M.; Okada, Y. *Am. J. Pathol.* 1996, 148, 611; Gress, T.M.; Mueller-Pillasch, F.; Lerch, M.M.; Friess, H.; Buechler, M.; Adler, G. *Int. J. Cancer*, 1995, 62, 407; Kawashima, A.; Nakanishi, I.; Tsuchiya, H.; Roessner, A.; Obata, K.; Okada, Y. *Virchows Arch.*,

15 1994, 424, 547-552.]. Angiogenesis, required for the growth of solid tumors, has also recently been shown to have a gelatinase component to its pathology [Crawford, H.C; Matrisian, L.M. *Invasion Metast.* 1994-95, 14, 234; Ray, J.M.; Stetler-Stevenson, W.G. *Exp. Opin. Invest. Drugs*, 1996, 5, 323.]. Furthermore, there is evidence to suggest that gelatinase is involved in plaque rupture associated with atherosclerosis

20 [Dollery, C.M.; McEwan, J.R.; Henney, A.M. *Circ. Res.* 1995, 77, 863; Zempo, N.; Koyama, N.; Kenagy, R.D.; Lea, H.J.; Clowes, A.W. *Arterioscler. Thromb. Vasc. Biol.* 1996, 16, 28; Lee, R.T.; Schoen, F.J.; Loree, H.M.; Lark, M.W., Libby, P. *Arterioscler. Thromb. Vasc. Biol.* 1996, 16, 1070.]. Other conditions mediated by MMPs are restenosis, MMP-mediated osteopenias, inflammatory diseases of the

25 central nervous system, skin aging, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound healing, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel

30 disease, periodontal disease, age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neovascularization and corneal graft rejection.

The hypothesis that MMPs are important mediators of the tissue destruction

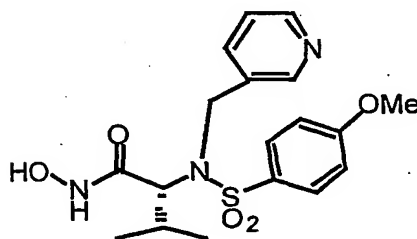
35 that occurs in arthritis has long been considered, since it was first recognized that these enzymes are capable of degrading collagens and proteoglycans which are the

major structural components of cartilage [Sapolsky, A.I.; Keiser, H.; Howell, D.S.; Woessner, J.F., Jr.; *J. Clin. Invest.* 1976, 58, 1030; Pelletier, J.-P.; Martel-Pelletier, J.; Howell, D.S.; Ghandur-Mnaymneh, L.; Enis, J.E.; Woessner, J.F., Jr., *Arthritis Rheum.* 1983, 26, 63.], and continues to develop as new MMPs are identified. For example, collagenase-3 (MMP-13) was cloned from breast cancer cells in 1994, and the first report that it could be involved in arthritis appeared in 1995 [Freiji, J.M.; Diez-Itza, I.; Balbin, M.; Sanchez, L.M.; Blasco, R.; Tolivia, J.; Lopez-Otin, C. *J. Biol. Chem.* 1994, 269, 16766; Flannery, C.R.; Sandy, J.D. 102-17, 41st Ann. Meet. Orth. Res. Soc. Orlando, FL. February 13-16, 1995.]. Evidence is accumulating that implicates MMP-13 in the pathogenesis of arthritis. A major structural component of articular cartilage, type II collagen, is the preferred substrate for MMP-13 and this enzyme is significantly more efficient at cleaving type II collagen than the other collagenases [Knauper, V.; Lopez-Otin, C.; Smith, B.; Knight, G.; Murphy, G. *J. Biol. Chem.*, 1996, 271, 1544-1550; Mitchell, P.G.; Magna, H.A.; Reeves, L.M.; Lopresti-Morrow, L.L.; Yocum, S.A.; Rosner, P.J.; Geoghegan, K.F.; Hambor, J.E. *J. Clin. Invest.* 1996, 97, 761.]. MMP-13 is produced by chondrocytes, and elevated levels of MMP-13 has been found in human osteoarthritic tissues [Reboul, P.; Pelletier, J.-P.; Hambor, J.; Magna, H.; Tardif, G.; Cloutier, J.-M.; Martel-Pelletier, J. *Arthritis Rheum.* 1995, 38 (Suppl. 9), S268; Shlopov, B.V.; Mainardi, C.L.; Hasty, K.A. *Arthritis Rheum.* 1995, 38 (Suppl. 9), S313; Reboul, P.; Pelletier, J.-P.; Tardif, G.; Cloutier, J.-M.; Martel-Pelletier, J. *J. Clin. Invest.* 1996, 97, 2011]. Potent inhibitors of MMPs were described over 10 years ago, but the poor bioavailability of these early peptidic, substrate mimetic MMP inhibitors precluded their evaluation in animal models of arthritis. More bioavailable, non-peptidic MMP inhibitors may be preferred for the treatment of diseases mediated by MMPs.

It is expected that small molecule inhibitors of gelatinase therefore have the potential for treating a variety of disease states. While a variety of MMP inhibitors have been identified and disclosed in the literature, the vast majority of these molecules are peptidic or peptide-like compounds that may have bioavailability and pharmacokinetic problems that would limit their clinical effectiveness. Low molecular weight, potent, long-acting, orally bioavailable inhibitors of gelatinases and collagenases are therefore highly desirable for the potential chronic treatment of the above mentioned disease states. Several non-peptidic, sulfur-containing hydroxamic acids have recently been disclosed and are listed below.

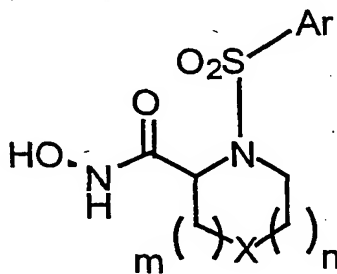
U. S. patents 5,455,258, 5,506,242 and 5,552,419, as well as European patent application EP606,046A1 and WIPO international publications WO96/00214 and

WO97/22587 disclose non-peptide matrix metalloproteinase inhibitors of which the compound CGS27023A is representative. The discovery of this type of MMP inhibitor is further detailed by MacPherson, *et. al.* in *J. Med. Chem.*, (1997), 40, 2525. Additional publications disclosing sulfonamide based MMP inhibitors which are
5 variants of the sulfonamide-hydroxamate shown below, or the analogous sulfonamide-carboxylates, are European patent application EP-757984-A1 and WIPO international publications WO95/35275, WO95/35276, WO96/27583, WO97/19068 and WO97/27174.

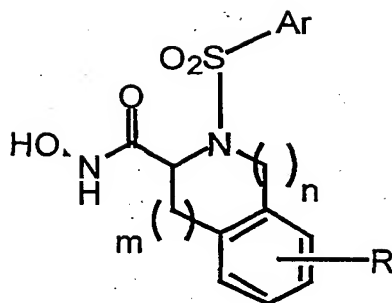


CGS 27023A

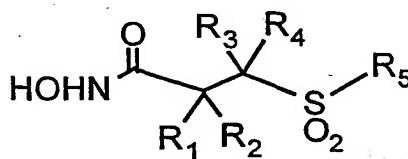
Publications disclosing β -sulfonamide-hydroxamate MMP inhibitor analogs of CGS 27023A in which the carbon alpha to the hydroxamic acid has been joined in a ring to the sulfonamide nitrogen, as shown below, include WIPO international
15 publications WO96/33172 and WO97/20824.



The German patent application DE19,542,189-A1 discloses additional
20 examples of cyclic sulfonamides as MMP inhibitors. In this case the sulfonamide-containing ring is fused to a phenyl ring to form an isoquinoline.



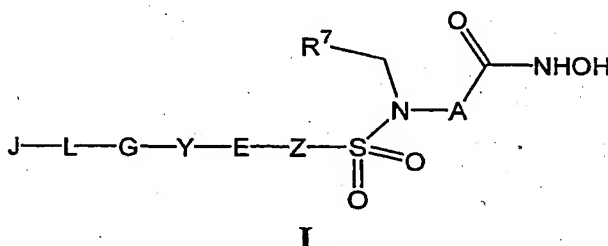
5 Analogues of the sulfonamide-hydroxamate MMP inhibitors in which the
 sulfonamide nitrogen has been replaced by a carbon atom, as shown in the general
 structure below, are European patent application EP-780386-A1 and WIPO
 international publication WO97/24117.



10 Certain ortho-sulfonamido aryl hydroxamic acids are described in US patent
 5929097, WO9816514 and WO9816520.

Description of the Invention

15 The MMP inhibiting ortho-sulfonamido aryl hydroxamic acids of the present
 invention are represented by formula I



20 where the hydroxamic acid moiety and the sulfonamido moiety are bonded to
 adjacent carbons of A where:

A is aryl, heteroaryl or heteroaryl fused to a phenyl ring;

Z is aryl, heteroaryl, or heteroaryl fused to a phenyl;

E and G are independently CH₂, NR⁵, or O, or S or a bond:

Y is cycloalkyl, cycloheteroalkyl, -C₁-C₅-perfluoroalkyl, alkyl, alkenyl, alkynyl, heteroalkyl, alkylaryl, or heteroaryl;

J is aryl, heteroaryl, heteroaryl fused to a phenyl, cycloalkyl, cycloheteroalkyl, -C₁-C₅-perfluoroalkyl, alkyl, alkenyl, or alkynyl;

R⁵ and R⁶ are independently H, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, -C₁-C₄-perfluoroalkyl, alkyl, alkenyl, or alkynyl;

R⁷ is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl or 3-6 membered cycloheteroalkyl;

or

R⁷CH₂-N-A- can form a non-aromatic 1,2-benzo-fused 7-10 membered heterocyclic ring optionally containing an additional heteroatom selected from O, S and N wherein said heterocyclic ring may be optionally fused to another benzene ring;

L is -C(O)-, S(O)_y, -NR⁵C(O)NR⁶-, -NR⁵C(O)O-, -OC(O)NR⁵-, -SC(O)-, -C(O)S-, -NR⁵C(O)-, -C(O)NR⁵-, -SC(O)NR⁵-, -NR⁵C(O)S-, -OC(O)O-;

y is 1 or 2;

and the pharmaceutically acceptable salts thereof and the optical isomers and diastereomers thereof.

Preferred compounds of the invention are those wherein:

A is aryl, heteroaryl or heteroaryl fused to a phenyl ring optionally substituted by one or more of R¹, R², R³ and R⁴ the same or different;

Z is aryl, heteroaryl, or heteroaryl fused to a phenyl, optionally substituted by one or more of R¹⁰, R¹¹, R¹² and R¹³ the same or different;

R¹, R², R³, R⁴, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, R³⁰ and R³¹ are independently -H, -COR⁵, -F, -Br, -Cl, -I, C(O)NR⁵OR⁶, -CN, -OR⁵, -C₁-C₄-perfluoroalkyl, -S(O)_xR⁵, -OPO(OR⁵)OR⁶, -PO(OR⁶)R⁵, -OC(O)NR⁵R⁶, -COOR⁵, -CONR⁵R⁶, -SO₃H, -NR⁵R⁶, -NR⁵COR⁶, -NR⁵COOR⁶, -SO₂NR⁵R⁶, -NO₂, -N(R⁵)SO₂R⁶,

NR⁵CONR⁵R⁶NR⁵C(=NR⁶)NR⁵R⁶, 3-6 membered cycloheteroalkyl, aryl, heteroaryl, biphenyl, -SO₂NHCOR¹⁸, -CONHSO₂R¹⁸, -tetrazol-5-yl, -SO₂NHCN, -SO₂NHCONR⁵R⁶ or straight chain or branched -C₁-C₆ alkyl, -C₂-C₆-alkenyl, or -

C₂-C₆-alkynyl, or -C₃-C₆-cycloalkyl, each optionally substituted with -COR⁵, -CN, -C₂-C₆ alkenyl, -C₂-C₆ alkynyl, -OR⁵, -C₁-C₄-perfluoroalkyl, -S(O)_xR⁵, -OC(O)NR⁵R⁶, -COOR⁵, -CONR⁵R⁶, -SO₃H, -NR⁵R⁶, -NR⁵COR⁶, -NR⁵COOR⁶, -SO₂NR⁵R⁶, -NO₂, -N(R⁵)SO₂R⁶, -NR⁵CONR⁵R⁶, -C₃-C₆cycloalkyl, 3-6 membered
 5 cycloheteroalkyl, aryl, heteroaryl, biphenyl, -SO₂NHCOR¹⁸, -CONHSO₂R¹⁸; -PO(OR⁵)OR⁶, -PO(OR⁶)R⁵, -tetrazol-5-yl, C(O)NR⁵OR⁶, -NR⁵C(=NR⁶)NR⁵R⁶, -SO₂NHCONR⁵R⁶ or -SO₂NHCN; or

when any of R¹ and R², or R¹⁰ and R¹¹ or R¹⁴ and R¹⁵ are on adjacent carbons of A or J or Z respectively, then each pair of R¹ and R², or R¹⁰ and R¹¹ or
 10 R¹⁴ and R¹⁵ together with the carbons to which they are attached can form a 5 to 7 membered saturated or unsaturated heterocyclic ring, a 5-6 membered heteroaryl ring, or a 5 to 7 membered saturated or unsaturated carbocyclic ring;

x is 0-2;

E and G are independently CH₂, NR⁵, or O, or S or a bond:

15 Y is -C₃-C₆-cycloalkyl, -C₃-C₆-cycloheteroalkyl, -C₁-C₅-perfluoroalkyl, straight chain or branched -C₁-C₆ alkyl, straight or branched chain -C₂-C₆-alkenyl, or straight or branched chain C₂-C₆-alkynyl or heteroalkyl, alkylaryl, heteroaryl optionally substituted with R²⁰, R²¹, R²², and R²³;

J is aryl, heteroaryl, or heteroaryl fused to a phenyl; optionally substituted
 20 with R¹⁴, R¹⁵, R¹⁶, and R¹⁷ or -C₃-C₆-cycloalkyl, -C₃-C₆-cycloheteroalkyl, -C₁-C₅-perfluoroalkyl, straight chain or branched -C₁-C₆ alkyl, straight or branched chain -C₂-C₆-alkenyl, or straight or branched chain C₂-C₆-alkynyl;

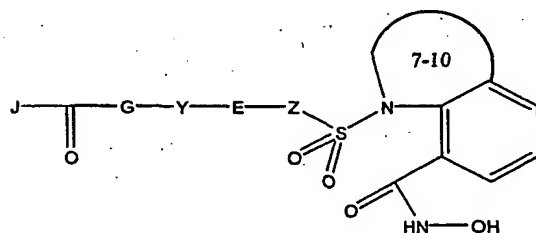
R⁵ and R⁶ are independently H, aryl, heteroaryl, -C₃-C₆-cycloalkyl, -C₃-C₆-cycloheteroalkyl, -C₁-C₄-perfluoroalkyl, or straight chain or branched -C₁-C₆ alkyl, -
 25 C₂-C₆-alkenyl, or -C₂-C₆-alkynyl, each optionally substituted with -OH, -COR⁸, -CN, -C(O)NR⁸OR⁹, -C₂-C₆-alkenyl, -C₂-C₆-alkynyl, -OR⁸, -C₁-C₄-perfluoroalkyl, -S(O)_xR⁸, -OPO(OR⁸)OR⁹, -PO(OR⁸)R⁹, -OC(O)NR⁸R⁹, -COOR⁸, -CONR⁸R⁹, -SO₃H, -NR⁸R⁹, -NCOR⁸R⁹, -NR⁸COOR⁹, -SO₂NR⁸R⁹, -NO₂, -N(R⁸)SO₂R⁹, -NR⁸CONR⁸R⁹, -C₃-C₆ cycloalkyl, 3-6 membered cycloheteroalkyl, aryl, heteroaryl, -
 30 SO₂NHCOR¹⁹, -CONHSO₂R¹⁹, -tetrazol-5-yl, NR⁸C(=NR⁹)NR⁸R⁹, -SO₂NHCONR⁸R⁹, or -SO₂NHCN;

R^7 is hydrogen, straight chain or branched $-C_1-C_6$ -alkyl, $-C_2-C_6$ -alkenyl, or $-C_2-C_6$ -alkynyl each optionally substituted with $-OH$, $-COR^5$, $-CN$, $-C_2-C_6$ -alkenyl, $-C_2-C_6$ -alkynyl, $-OR^5$, $-C_1-C_4$ -perfluoroalkyl, $-S(O)_xR^5$, $OPO(OR^5)OR^6$, $-PO(OR^5)R^6$, $-OC(O)NR^5R^6$, $-COOR^5$, $-CONR^5R^6$, $-SO_3H$, $-NR^5R^6$, $-NR^5COR^6$,
 5 $-NR^5COOR^6$, $-SO_2NR^5R^6$, $-NO_2$, $-N(R^5)SO_2R^6$, $-NR^5CONR^5R^6$, $-C_3-C_6$ cycloalkyl, $-C_3-C_6$ -cycloheteroalkyl, -aryl, heteroaryl, $-SO_2NHCOR^{32}$, $-CONHSO_2R^{32}$,
 $-tetrazol-5-yl$, $-NR^5C(=NR^6)NR^5R^6$, $-C(O)NR^5OR^6$, $-SO_2NHCONR^5R^6$ or $-SO_2NHCN$;

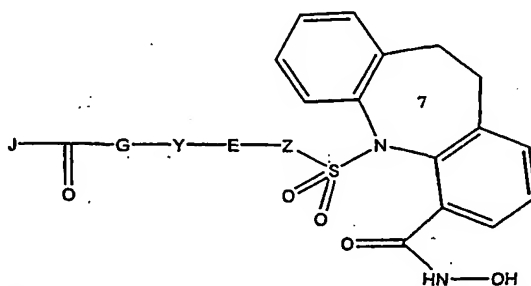
or R^7 is phenyl or naphthyl, optionally substituted by R^{24} , R^{25} , R^{26} and R^{27} or a 5 to 6 membered heteroaryl group optionally substituted by R^{28} , R^{29} , R^{30} and R^{31} ; or

R^7 is C_3-C_6 cycloalkyl or 3-6 membered cycloheteroalkyl; or

R^7CH_2-N-A - (where R^7 is bonded to A) can form a non-aromatic 1,2-benzo-fused 7-10 membered heterocyclic ring optionally containing an additional heteroatom selected from O, S and N wherein said heterocyclic ring may be
 15 optionally fused to another benzene ring such as for example:



or (fused):



20 R^8 and R^9 are independently H, aryl or heteroaryl, $-C_3-C_7$ cycloalkyl or 3 to 6 membered cycloheteroalkyl, $-C_1-C_4$ -perfluoroalkyl, straight chain or branched $-C_1-C_6$ -alkyl, $-C_2-C_6$ -alkenyl, or $-C_2-C_6$ -alkynyl, each optionally substituted with hydroxy, alkoxy, aryloxy, $-C_1-C_4$ -

perfluoroalkyl, amino, mono- and di-C₁-C₆-alkylamino, carboxylic acid, carboalkoxy and carboaryloxy, nitro, cyano, carboxamido primary, mono- and di-C₁-C₆-alkylcarbamoyl;

R¹⁸ and R³² are independently aryl, heteroaryl, -C₃-C₆-cycloalkyl, -C₃-C₆-cycloheteroalkyl, -C₁-C₄-perfluoroalkyl, or straight chain or branched -C₁-C₆ alkyl, -C₂-C₆-alkenyl, or -C₂-C₆-alkynyl, each optionally substituted with -OH, -COR⁸, -CN, -C(O)NR⁸OR⁹, -C₂-C₆-alkenyl, -C₂-C₆-alkynyl, -OR⁸, -C₁-C₄-perfluoroalkyl, -S(O)_xR⁸, -OPO(OR⁸)OR⁹, -PO(OR⁸)R⁹, -OC(O)NR⁸R⁹, -COOR⁸, -CONR⁸R⁹, -SO₃H, -NR⁸R⁹, -NCOR⁸R⁹, -NR⁸COOR⁹, -SO₂NR⁸R⁹, -NO₂, -N(R⁸)SO₂R⁹, -NR⁸CONR⁸R⁹, -C₃-C₆ cycloalkyl, 3-6 membered cycloheteroalkyl, aryl, heteroaryl, -SO₂NHCOR¹⁹, -CONHSO₂R¹⁹, -tetrazol-5-yl, NR⁸C(=NR⁹)NR⁸R⁹, -SO₂NHCONR⁸R⁹, or -SO₂NHCN;

R¹⁹ is aryl or heteroaryl, -C₃-C₇cycloalkyl or 3 to 6 membered cycloheteroalkyl, -C₁-C₄-perfluoroalkyl, straight chain or branched -C₁-C₆-alkyl, -C₂-C₆-alkenyl, or -C₂-C₆-alkynyl, each optionally substituted with hydroxy, alkoxy, aryloxy, -C₁-C₄-perfluoroalkyl, amino, mono- and di-C₁-C₆-alkylamino, carboxylic acid, carboalkoxy and carboaryloxy, nitro, cyano, carboxamido primary, mono- and di-C₁-C₆-alkylcarbamoyl;

L is -C(O)-, S(O)_y, -NR⁵C(O)NR⁶-, -NR⁵C(O)O-, -OC(O)NR⁵-, -SC(O)-, -C(O)S-, -NR⁵C(O)-, -C(O)NR⁵-, -SC(O)NR⁵-, -NR⁵C(O)S-, -OC(O)O-;

y is 1 or 2;

and the pharmaceutically acceptable salts thereof and the optical isomers and diastereomers thereof.

It is preferred in some embodiments of the invention that both of the carbons of A adjacent to the carbon bearing the sulfonamido group have a substituent other than hydrogen.

Examples of A are phenyl optionally substituted by C₁-C₆ straight or branched chain alkyl.

Examples of Z are phenyl, e.g. where E is *para* to the -SO₂- group.

In accordance with some preferred embodiments of the present invention, E and G are independently selected from NH, O and S. In other preferred embodiments of the present invention E is O and G is NH.

In other preferred embodiments Y is C₁-C₆ straight chain alkyl, and more preferably C₂-C₃ straight chain alkyl.

In some embodiments of the present invention E and G are independently selected from CH₂, NH, O and S and Y is -C₁-C₄-perfluoroalkyl, or straight chain or
5 branched -C₁-C₆ alkyl, -C₂-C₆-alkenyl, or C₂-C₆-alkynyl.

In still other embodiments of the present invention, E and G are independently selected from CH₂, NH, O and S and Y is straight chain or branched -C₁-C₆ alkyl.

When G is CH₂, in some embodiments of the invention, it is preferred that Y is - C₂-C₅ -perfluoroalkyl, or straight chain or branched -C₁-C₆ alkyl,

10 In still other embodiments of the present invention, E and G are CH₂, and Y is straight chain or branched -C₁-C₆ alkyl, and more preferably Y is straight chain or branched -C₁-C₅ alkyl.

J is preferably heteroaryl fused to a phenyl and particularly preferred is where J is benzofuranyl, benzothienyl and quinoliny. J may be indolyl.

15 When R¹⁴ and R¹⁵ are on adjacent atoms of J, R¹⁴, R¹⁵ and J may together preferably form a bicyclic oxygen containing aryl moiety such as benzodioxanyl or benzodioxlyl.

Preferred compounds of the present invention include:

20 Quinoline-2-carboxylic acid (2-{4-[(2-hydroxycarbamoyl-6-methyl-phenyl)-methyl-sulfamoyl]-phenoxy}-ethyl)-amide

Benzofuran-2-carboxylic acid (3-{4-[(2-hydroxycarbamoyl-6-methyl-phenyl)-methyl-sulfamoyl]-phenoxy}-propyl)-amide

25 Benzofuran-2-carboxylic acid (4-{4-[(2-hydroxycarbamoyl-6-methyl-phenyl)-methyl-sulfamoyl]-phenoxy}-butyl)-amide

1H-Indole-2-carboxylic acid (3-{4-[(2-hydroxycarbamoyl-6-methyl-phenyl)-methyl-sulfamoyl]-phenoxy}-propyl)-amide

Benzo[b]thiophene-2-carboxylic acid (2-{4-[(2-hydroxycarbamoyl-6-methyl-phenyl)-methyl-sulfamoyl]-phenoxy}-ethyl)-amide

30 N-{3-[4-({2-[(Hydroxyamino)carbonyl]-6-dimethylanilino}sulfonyl)-phenoxy]propyl}-1,3-benzodioxole-5-carboxamide

N-{4-[4-({2-[(Hydroxyamino)carbonyl]-6-dimethylanilino}sulfonyl)-phenoxy]butyl}-1,3-benzodioxole-5-carboxamide

35 N-{3-[4-({2-[(Hydroxyamino)carbonyl]-6-dimethylanilino}-sulfonyl)-phenoxy]propyl}-1-benzothiophene-2-carboxamide

Benzofuran-2-carboxylic acid (2-{4-[benzyl-(2-hydroxycarbamoyl-4,6-dimethyl-phenyl)-sulfamoyl]-phenoxy}-ethyl)-amide.

Halogen, as used herein means fluoro, chloro, bromo and iodo.

5 Alkyl as used herein means a branched or straight chain radical having from 1 to 20 carbon atoms optionally substituted with one or more groups selected from halogen, cyano, nitro, hydroxy, sulfhydryl, amino, alkylamino, dialkylamino, alkoxy, aryloxy, thioalkyl, thioaryl, acyl, aroyl, acyloxy, acylamino, carboxy, carboxyalkyl, carboxyaryl, carboxamido, carboxamidoalkyl, carboxamidodialkyl, alkylsulfonamido, 10 arylsulfonamido, aryl, heteroaryl, and more preferably from 1 to 6 carbon atoms also optionally substituted. Exemplary alkyl groups include but are not limited to methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl also optionally substituted as well as perfluoroalkyl.

Alkenyl as used herein means a branched or straight chain radical having from 15 2 to 20 carbon atoms optionally substituted with one or more groups selected from halogen, cyano, nitro, hydroxy, sulfhydryl, amino, alkylamino, dialkylamino, alkoxy, aryloxy, thioalkyl, thioaryl, acyl, aroyl, acyloxy, acylamino, carboxy, carboxyalkyl, carboxyaryl, carboxamido, carboxamidoalkyl, carboxamidodialkyl, alkylsulfonamido, arylsulfonamido, aryl, heteroaryl, and more preferably from 2 to 6 carbon atoms, with 20 the chain containing at least one carbon-carbon double bond. Alkenyl, may be used synonymously with the term olefin and includes alkylidenes. Exemplary alkenyl groups include but are not limited to ethylene, propylene and isobutylene.

Alkynyl as used herein means a branched or straight chain radical having from 2 to 20 carbon atoms optionally substituted with one or more groups selected from 25 halogen, cyano, nitro, hydroxy, sulfhydryl, amino, alkylamino, dialkylamino, alkoxy, aryloxy, thioalkyl, thioaryl, acyl, aroyl, acyloxy, acylamino, carboxy, carboxyalkyl, carboxyaryl, carboxamido, carboxamidoalkyl, carboxamidodialkyl, alkylsulfonamido, arylsulfonamido, aryl, heteroaryl, and more preferably from 3 to 10 carbon atoms, with the chain containing at least one carbon-carbon triple bond.

30 Alkoxy as used herein means an alkyl-O- group in which the alkyl group is as previously described. Exemplary alkoxy groups include but are not limited to methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, and t-butoxy.

Aryl as used herein refers to phenyl or naphthyl which may be optionally substituted as described above (e.g. R¹⁻⁴, R¹⁰⁻¹³, R¹⁴⁻¹⁷ etc.,) such as with one to four 35 substituents selected from the group of alkyl, halogen, cyano, nitro, hydroxy, sulfhydryl, amino, alkylamino, dialkylamino, alkoxy, aryloxy, thioalkyl, thioaryl,

acyl, aroyl, acyloxy, acylamino, carboxy, carboxyalkyl, carboxyaryl, carboxamido, carboxamidoalkyl, carboxamidodialkyl, alkylsulfonamido, arylsulfonamido, aryl, or heteroaryl..

Heteroaryl, as used herein refers to a 5-6 membered heteroaromatic ring having from 1 to 3 heteroatoms independently selected from N, NH, O and S. Heteroaryl may be optionally substituted with substituents as described above (e.g. R¹⁻⁴, R¹⁰⁻¹³, R¹⁴⁻¹⁷) such as selected from the group halogen, cyano, nitro, hydroxy, sulfhydryl, amino, alkylamino, dialkylamino, alkoxy, aryloxy, thioalkyl, thioaryl, acyl, aroyl, acyloxy, acylamino, carboxy, carboxyalkyl, carboxyaryl, carboxamido, carboxamidoalkyl, carboxamidodialkyl, alkylsulfonamido, arylsulfonamido, aryl, and heteroaryl. Heteroaryl includes, but is not limited to pyrrole, furan, thiophene, pyridine, pyrimidine, pyridazine, pyrazine, triazole, pyrazole, imidazole, isothiazole, thiazole, isoxazole and oxazole.

Cycloalkyl or saturated or unsaturated carbocyclic ring, refers to a cyclic alkyl group having from 3 to 7 carbon atoms and may include from 1 to 2 double bonds. Cycloalkyl groups may be optionally substituted.

Cycloheteroalkyl, as used herein refers to 3 to 7 membered saturated or unsaturated heterocyclic ring having one to three heteroatoms independently selected from N, NH, O, and S and optionally having 1 or 2 double bonds. Cycloheteroalkyl groups may be optionally substituted with from one to three groups. The term heterocycloalkyl or heterocyclic ring includes, but is not limited to oxazolidine, thiazolidine, imidazolidine, tetrahydrofuran, tetrahydrothiophene, tetramethylene sulfone, dihydropyran, tetrahydropyran, piperidine, pyrrolidine, dioxane, morpholine, azepine and diazepine.

The term "heteroaryl fused to a phenyl" includes, but is not limited to, benzoxazole, benzoisoxazole, indole, isoindole, benzothiophene, benzofuran, quinoline, quinazoline, quinoxaline, benzotriazole, benzimidazole, benzthiazole, benzopyrazole and isoquinoline. Substitutions may occur on one or both rings.

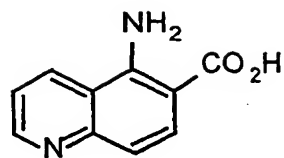
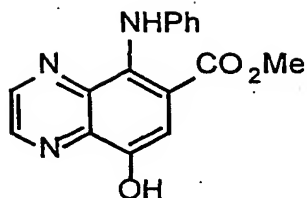
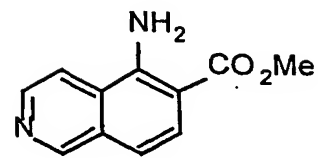
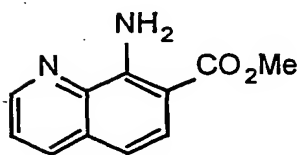
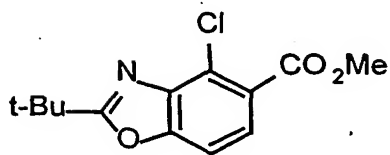
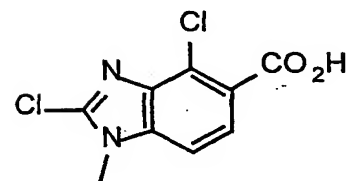
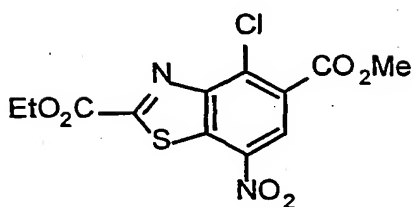
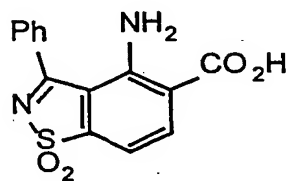
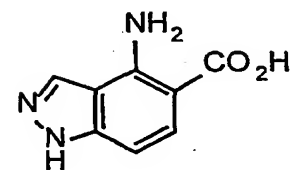
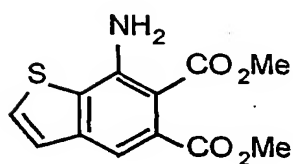
Pharmaceutical acceptable salts are encompassed by the present invention and include, as appropriate, inorganic and organic salts. Exemplary acid salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate,

persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, mesylate and undecanoate.

5 Other compounds that are acids can also form salts with alkali metals or alkali earth metals, such as sodium, potassium, calcium, or magnesium, or with organic bases or basic quaternary ammonium salts.

The compounds according to the invention can be in various stereoisomeric forms such as enantiomers or diastereomers. The invention includes optically pure forms of compounds of the present invention prepared in accordance with known methods.

10 The following compounds (1-10) which may be used in preparing invention compounds are known and references are given hereinbelow.

12345678910

Compound 1:

- 5 a) Meyer, Michael D.; Altenbach, Robert J.; Basha, Fatima Z.; Carroll, William A.; Drizin, Irene; Elmore, Steven W.; Kerwin, Jr James F.; Lebold, Suzanne A.; Lee, Edmund L.; Sippy, Kevin B.; Tietje, Karin R.; Wendt, Michael D. Tricyclic substituted hexahydrobenz[e]isoindole alpha-1 adrenergic antagonists. US 5597823. CAN 126:199575.
- 10 b) Meyer, Michael D.; Altenbach, Robert J.; Basha, Fatima Z.; Carroll, William A.; Drizin, Irene; Kerwin, James F., Jr.; Lebold, Suzanne A.; Lee, Edmund L.; Elmore,

Steven W.; et al. Preparation of tricyclic substituted benz[e]isoindoles as $\alpha 1$ adrenergic antagonists. PCT Int. Appl WO 9622992 A1 CAN 125:221858.

Compound 2:

5 Troll, Theodor; Schmid, Klaus. Preparation and reactions of a 2H-pyrrolo[3,4-b]pyridine and a 2H-pyrrolo[3,4-b]pyrazine. J. Heterocycl. Chem. (1986), 23(6), 1641-4.

Compound 3:

10 Meyer, Michael D.; Altenbach, Robert J.; Basha, Fatima Z.; Carroll, William A.; Drizin, Irene; Elmore, Steven W.; Kerwin, Jr James F.; Lebold, Suzanne A.; Lee, Edmund L.; Sippy, Kevin B.; Tietje, Karin R.; Wendt, Michael D. Tricyclic substituted hexahydrobenz[e]isoindole α -1 adrenergic antagonists. US 5597823. CAN 126:199575.

Compound 4:

15 a) Meyer, Michael D.; Altenbach, Robert J.; Basha, Fatima Z.; Carroll, William A.; Drizin, Irene; Elmore, Steven W.; Kerwin, Jr James F.; Lebold, Suzanne A.; Lee, Edmund L.; Sippy, Kevin B.; Tietje, Karin R.; Wendt, Michael D. Tricyclic substituted hexahydrobenz[e]isoindole α -1 adrenergic antagonists. US 5597823. CAN 126:199575.

20 b) Meyer, Michael D.; Altenbach, Robert J.; Basha, Fatima Z.; Carroll, William A.; Drizin, Irene; Kerwin, James F., Jr.; Lebold, Suzanne A.; Lee, Edmund L.; Elmore, Steven W.; et al. Preparation of tricyclic substituted benz[e]isoindoles as $\alpha 1$ adrenergic antagonists. PCT Int. Appl. WO 9622992 A1 CAN 125:221858.

Compound 5:

25 Geach, Neil; Hawkins, David William; Pearson, Christopher John; Smith, Philip Henry Gaunt; White, Nicolas. Preparation of isoxazoles as herbicides. Eur. Pat. Appl. EP 636622 A1 CAN 122:290845.

Compound 6:

30 Kotovskaya, S. K.; Mokrushina, G. A.; Suetina, T. A.; Chupakhin, O. N.; Zinchenko, E. Ya.; Lesovaya, Z. I.; Mezentsev, A. S.; Chernyshov, A. I.; Samoilova, L. N. Benzimidazolyl derivatives of penicillin and cephalosporin: synthesis and antimicrobial activity. Khim.-Farm. Zh. (1989), 23(8), 952-6.

Compound 7:

Wagner, Klaus. Bactericidal and fungicidal 4-chlorobenzothiazoles. Ger. Offen. DE 2136924 CAN 78:111293.

35 Compound 8:

Eggensperger, Heinz; Diehl, Karl H.; Kloss, Wilfried. 2-Hydroxy-4-alkoxybenzophenones. Ger. DE 1768599 711223. CAN 76:85557.

Compound 9:

- 5 Lichtenthaler, Frieder W.; Moser, Alfred. Nucleosides. 44. Benzo-separated pyrazolopyrimidines: expeditious syntheses of [3,4-g]- and [3,4-h]-linked pyrazoloquinazolinones. Tetrahedron Lett. (1981), 22(44), 4397-400.

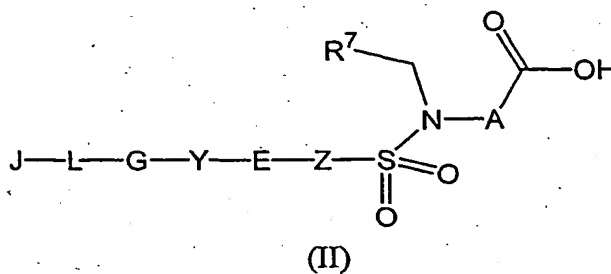
Compound 10:

- 10 Terpstra, Jan W.; Van Leusen, Albert M. A new synthesis of benzo[b]thiophenes and benzo[c]thiophenes by annulation of disubstituted thiophenes. J. Org. Chem. (1986), 51(2), 230-8.

The invention compounds may be prepared using conventional techniques known to those skilled in the art of organic synthesis.

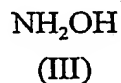
- 15 Accordingly this invention provides a process for preparing a compound of Formula I as defined above which comprises one of the following:

a) reacting a compound of formula II:



wherein J, L, G, Y, E, Z, A and R⁷ are defined above or a reactive derivative thereof, with a compound of formula III:

25



to give a corresponding compound of formula I;

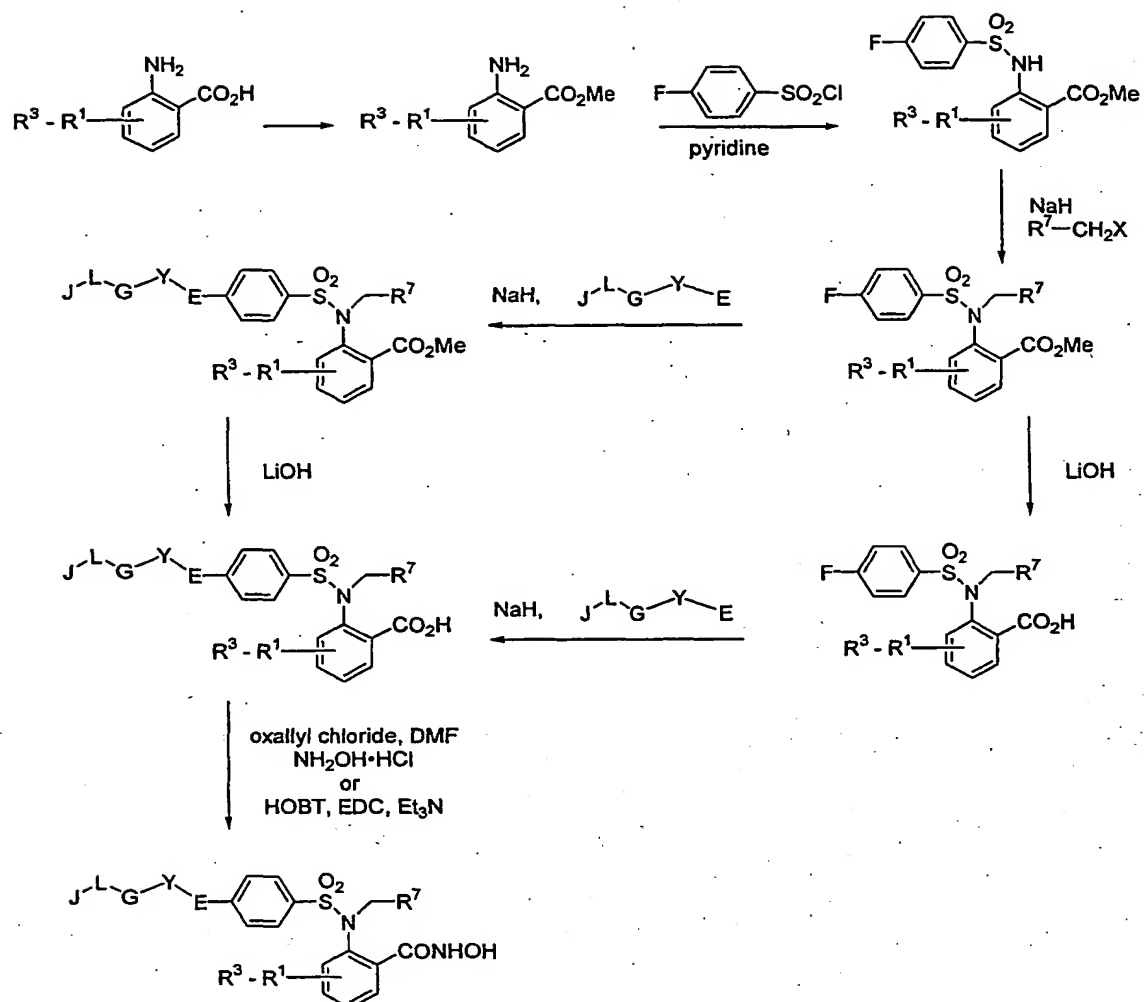
- b) resolving a mixture (e.g. racemate) of optically active isomers of a compound of formula I to isolate one enantiomer or diastereomer substantially free of the other enantiomer or diastereomers;
- 5 c) acidifying a basic compound of formula I with a pharmaceutically acceptable acid to give a pharmaceutically acceptable salt.

Means of coupling the carboxylic acid moiety to hydroxylamine are well known to those skilled in the art.

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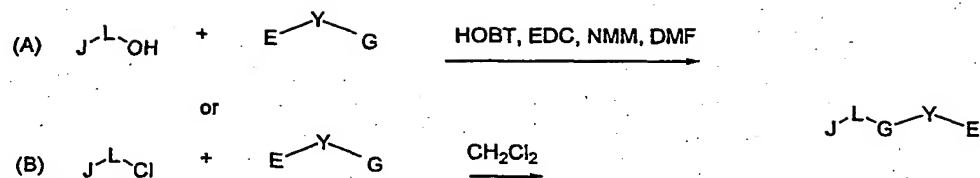
The following schemes (Scheme I and II) illustrates the general reaction sequence employed. For purposes of illustration only, wherein the group A is a phenyl, methyl anthranilate is reacted with p-fluorobenzenesulfonyl chloride to provide the requisite N-aryl sulfonamido-ester which is then alkylated to provide the N,N-disubstituted sulfonamide. This compound can then be converted into the elongated sulfonamide
15 by two routes. The N,N-disubstituted sulfonamide ester may be hydrolyzed to the carboxylic acid and then subjected to a nucleophilic displacement of the fluoro substituent, or it can be treated directly with a suitable nucleophile and subsequently hydrolyzed to the acid. The acid may then be converted into the corresponding
20 hydroxamic acid.

Scheme I



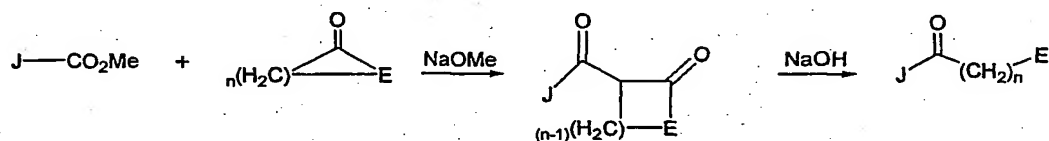
Scheme II depicts the preparation of suitable nucleophiles (for when E and G are independently N, O, or S and L is $-\text{C}(\text{O})-$ or $\text{S}(\text{O})_x$) employed in the displacement of the aryl fluoride.

Scheme II



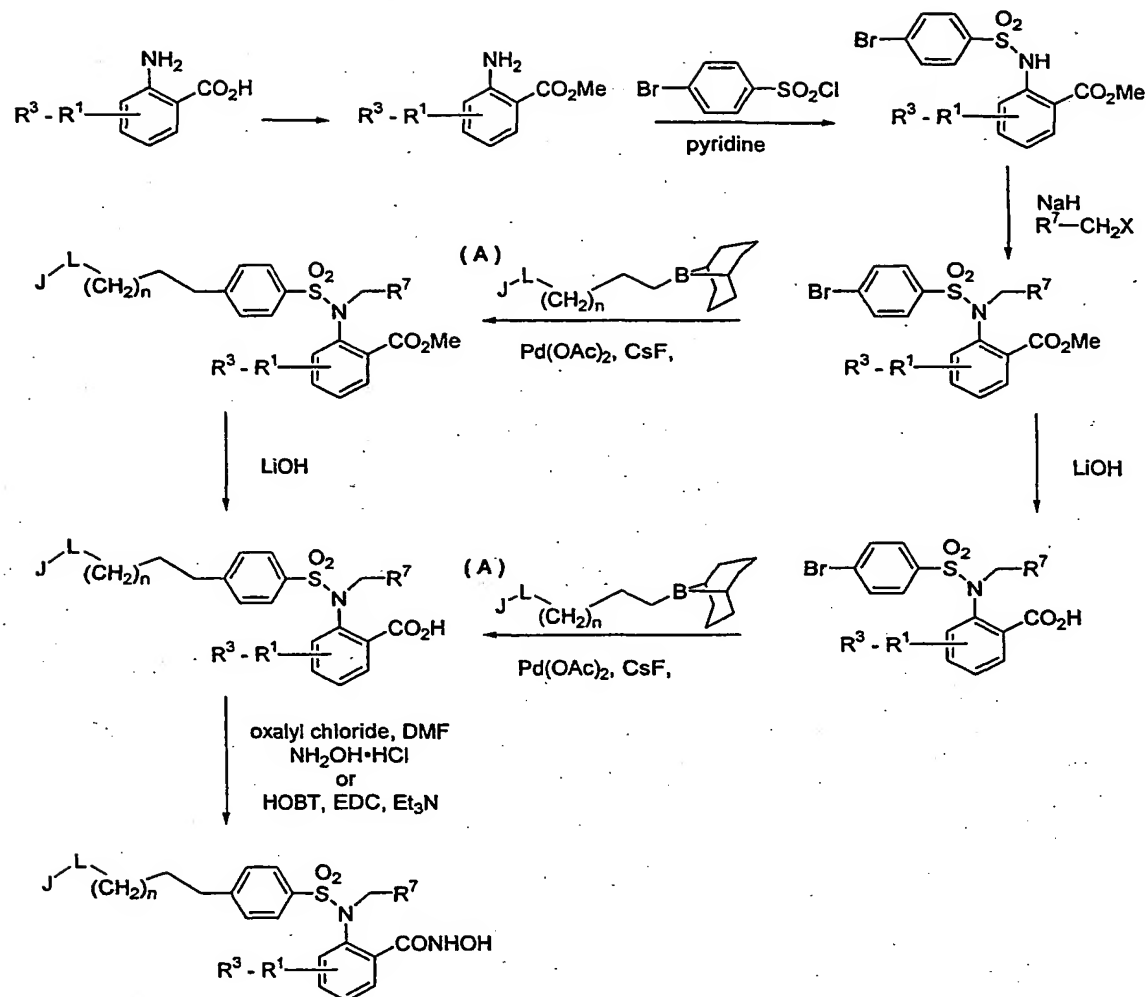
5 Alternatively, other nucleophiles for use in the displacement reaction (G is C) can be prepared via the route in Scheme III. A suitable ester is condensed with a lactone to provide a β -ketolactone. This lactone is then ring opened with concomitant decarboxylation to provide the requisite nucleophile for use in the displacement reaction.

10 Scheme III



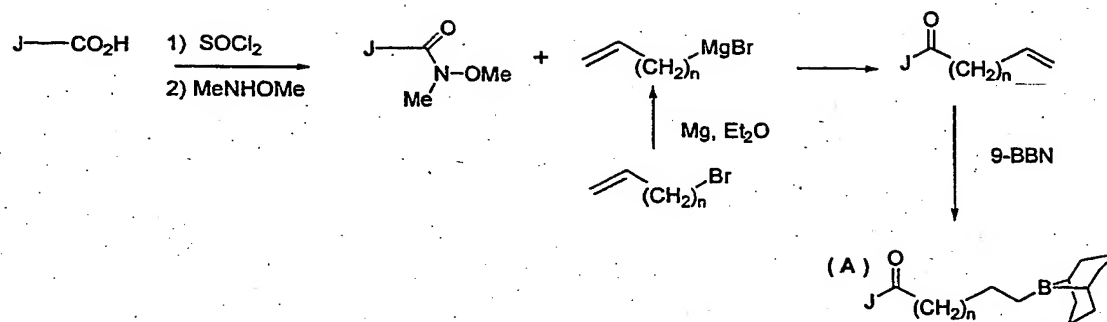
Alternatively, other compounds of the invention can be prepared via the route shown in Scheme 4. For purposes of illustration only, wherein the group A is shown as a phenyl, methyl anthranilate is reacted with p-bromobenzenesulfonyl chloride to provide the requisite N-aryl sulfonamido-ester which is then alkylated to provide the N,N-disubstituted sulfonamide. This compound can then be converted into the elongated sulfonamide by two routes. The N,N-disubstituted sulfonamide ester may be hydrolyzed to the carboxylic acid and then subjected to a palladium catalyzed coupling to a suitable alkyl boron reagent (compound A, prepared via the route depicted in Scheme 5), or it can be treated directly with a suitable alkyl boron reagent and subsequently hydrolyzed to the acid. The acid may then be converted into the corresponding hydroxamic acid.

Scheme 4



- 5 Compound A (where L is $-\text{C}(\text{O})-$) may be prepared via the following route. A precursor carboxylic acid is converted to the Weinreb amide via formation of the acid chloride and subsequent displacement with methoxymethyl amine. The amide is then treated with a grignard reagent, the olefin of which is subsequently hydroborated with 9-BBN for use in the palladium coupling reaction.

Scheme 5



5

In preferred embodiments of the invention, compounds of the present invention are particularly useful for the treatment of rheumatoid arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, bone disease and HIV infection.

10

Compounds of this invention may be provided to a patient in need thereof. They may be administered neat or with a pharmaceutical carrier to the patient or provided in the form of a pro-drug which will be converted by the patient. The pharmaceutical carrier may be solid or liquid and generally may be any pharmaceutically acceptable carrier.. Formulation of drugs is discussed, for example, in Hoover, J.E., *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easton, Pennsylvania, 1975.

15

Applicable solid carriers can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

20

25

Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic

30

solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators.

5 Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g., cellulose derivatives, preferable sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) and their derivatives, and oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration the carrier can
10 also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral
15 administration may be either liquid or solid composition form.

The compounds of this invention may be administered rectally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an
20 aerosol. The compounds of this invention may also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive
25 devices. The creams and ointments may be viscous liquid or semi-solid emulsions of either the oil in water or water in oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a
30 reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

The dosage to be used in the treatment of a specific patient suffering from a disease or condition in which MMPs and TACE are involved must be subjectively determined by the attending physician. The variables involved include the severity of
35 the dysfunction, and the size, age, and response pattern of the patient. Treatment will generally be initiated with small dosages less than the optimum dose of the

compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. Precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated and standard medical principles.

5 Preferably the pharmaceutical composition is in unit dosage form, e.g., as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage form can be packaged compositions, for example packed powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a
10 capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

The following specific examples are included for illustrative purposes and are not to be construed as limiting to this disclosure in any way. Other procedures useful
15 for the preparation of the compounds of this invention will be apparent to those skilled in the art of synthetic organic chemistry.

Example 1

Methyl 2-[[[(4-fluorophenyl)sulfonyl](methyl)amino] 3-methyl benzoate

20 Methyl 2-[[[(4-fluorophenyl)sulfonyl]amino] 3-methyl benzoate (3.0 g, 9.3 mmol) was dissolved in dimethylformamide (DMF) (30 ml) and cooled to 0 °C. Iodomethane (0.75 ml, 12.0 mmol) was added, followed by sodium hydride (0.4 g, 11 mmol, 60% dispersion in mineral oil) and the reaction was allowed to warm to room temperature. After 15 hours, the reaction was diluted with water and extracted 3 times
25 with ethyl acetate. The organics were combined, washed with brine, dried over MgSO₄, and concentrated in vacuo to provide 2.8 g (90%) of the N-methyl sulfonamide as a white solid. ¹H NMR (DMSO-d₆): δ 2.0 (s, CH₃), 3.25 (s, CH₃), 3.55 (s, CH₃), 7.1-7.57 (m, 5 Ar H), 7.69-7.73 (m, 2 Ar H). Electrospray Mass Spec: m/z 338.3 (M+H)⁺.

Example 2

Methyl 2-[[[(4-fluorophenyl)sulfonyl](methyl)amino] 3-methyl benzoic acid

The product of Example 1 (2.8 g, 8.3 mmol) and 0.4 g lithium hydroxide (LiOH) were added to 65 ml of a (1:1.5:1) mixture of tetrahydrofuran (THF):
methanol (MeOH) : water, and stirred at room temperature. After 15 hours, the
35 solution was neutralized with 1N HCl and extracted 3 times with dichloromethane (CH₂Cl₂). The organics were combined, washed with brine, dried over MgSO₄, and

concentrated in vacuo to provide 2.56 g (95 %) of the carboxylic acid as a white solid. ¹H NMR (DMSO-d₆): δ 1.9 (s, CH₃), 3.20 (s, CH₃), 7.35-7.46 (m, 4 Ar H) 7.55-7.58 (d, 1 Ar H), 7.69-7.74 (m, 2 Ar H). Electrospray Mass Spec: *m/z* 322.2 (M-H)⁺.

Example 3

5 **3-Methyl-2-[methyl[(4-[2-[(2-quinolyncarbonyl)amino]ethoxy]phenyl)sulfonyl]amino] benzoic acid**

Sodium hydride (0.1 g, 2.3 mmol, 60% dispersion in mineral oil) was added to DMF (5 ml) and stirred at room temperature 10 minutes. A solution of N-(2-hydroxyethyl) 2-quinolinecarboxamide (0.21 g, 0.99 mmol) in DMF (1 ml) was added followed by a solution of the product of Example 2 (0.3 g, 0.98 mmol) in DMF (1 ml). After 3 hours, the solution was diluted with ethyl acetate and a sticky solid was filtered off. The solid was taken up in water, and the solution was acidified with 1N HCl. Filtration of the resulting precipitate gave 0.29 g (49% yield) of white powder. ¹H NMR (DMSO-d₆): δ 1.9 (s, CH₃), 3.17 (s, CH₃), 3.75 (m, CH₂), 4.23 (m, CH₂), 7.1 (d, 2 Ar H) 7.29-7.30 (m, 2 Ar H), 7.52-7.58 (m, 2 Ar H), 7.71-7.76 (t, 1 Ar H), 7.86-7.91 (t, 1 Ar H), 8.0-8.2 (m, 3 Ar H), 8.57-8.60 (d, 1 Ar H), 8.9 (s, 1 Ar H) 9.1 (br t, NH), 12.9 (s, OH). Electrospray Mass Spec: m/z 520.2 (M+H)⁺.

Example 4

20 **Quinoline-2-carboxylic acid (2-{4-[(2-hydroxycarbamoyl-6-methyl-phenyl)-methyl-sulfamoyl]-phenoxy}-ethyl)-amide**

The product of Example 3 (0.17 g, 0.33 mmol) was dissolved in DMF (5 ml). 1-hydroxybenzotriazole (HOBT) (0.1 g, 0.8 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.17 g, 0.92 mmol), hydroxylamine hydrochloride (0.18 g, 2.64 mmol) and finally triethylamine (0.46 ml, 3.3 mmol) were added sequentially to the solution and allowed to stir at room temperature. After 15 hours, ethyl acetate was added and the resulting precipitate filtered and triturated from ethyl ether to give 0.99 g (36% yield) of the hydroxamic acid as a white powder. MP 114-121 °C; ¹H NMR (DMSO-d₆): δ 2.1 (s, CH₃), 3.14 (s, CH₃), 3.62 (m, CH₂), 3.8 (m, CH₂), 7.1 (d, 2 Ar H) 7.29-7.30 (m, 2 Ar H), 7.52-7.58 (d, 1 Ar H), 7.71-7.76 (m, 3 Ar H), 7.86-7.91 (t, 1 Ar H), 8.0-8.2 (m, 3 Ar H), 8.57-8.60 (d, 1 Ar H), 8.89 (s, NH) 9.1 (br t, NH), 11.0 (s, OH). Electrospray Mass Spec: *m/z* 535.2 (M+H)⁺.

Example 5

2-[(4-{3-[(Benzofuran-2-carbonyl)-amino]-propoxy}-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid

The product of Example 2 (0.442 g, 1.37 mmol) was coupled to N-(3-hydroxypropyl)-1-benzofuran-2-carboxamide (0.3 g, 1.37 mmol) using the procedure
5 of Example 3 to provide 0.37 g (53% yield) of an off white powder. MP 184-186 °C;
¹H NMR (DMSO-d₆): δ 1.9 (s, CH₃), 2.04 (t, CH₂), 3.16 (s, CH₃), 3.46 (q, CH₂), 4.0
(t, CH₂), 7.01 (d, 2 Ar H) 7.30-7.78 (m, 10 Ar H), 8.56 (t, NH), 12.4 (br s, OH).
Electrospray Mass Spec: *m/z* 523.2 (M+H)⁺.

Example 6

Benzofuran-2-carboxylic acid (3-{4-[(2-hydroxycarbamoyl-6-methyl-phenyl)-methyl-sulfamoyl]-phenoxy}-propyl)-amide

5 The product of Example 5 (0.172 g, 0.33 mmol) was converted to the hydroxamic acid using the procedure of Example 4 to provide 0.073 g (41% yield) of a white solid. MP 148-150 °C; ¹H NMR (DMSO-d₆): δ 2.1 (s, CH₃), 2.04 (t, CH₂), 3.06 (s, CH₃), 3.39 (q, CH₂), 4.0 (t, CH₂), 7.01 (d, 2 Ar H) 7.30-7.78 (m, 10 Ar H), 8.85 (t, NH), 8.89 (s, NH), 11.0 (s, OH). Electrospray Mass Spec: 538.1 *m/z* (M+H)⁺.

10

Example 7

2-[(4-{4-[(Benzofuran-2-carbonyl)-amino]-butoxy}-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid

15 The product of Example 2 (0.40 g, 1.24 mmol) was coupled to N-(4-hydroxybutyl)-1-benzofuran-2-carboxamide, prepared according to Example 17, (0.29 g, 1.24 mmol) using the procedure of Example 3 to provide 0.34 g (51% yield) of an off white powder. MP > 200 °C; ¹H NMR (DMSO-d₆): δ 1.35-1.62 (m, CH₂, CH₂), 1.9 (s, CH₃), 3.20 (s, CH₃), 3.32-3.41 (m, CH₂, CH₂), 7.0-7.1 (m, 4 Ar H), 7.35 (t, 1 Ar H), 7.45 (t, 1 Ar H), 7.54 (s, 1 Ar H), 7.65 (d, 1 Ar H), 7.77 (d, 1 Ar H), 7.92 (m, 3 Ar H) 8.8 (t, NH), . Electrospray Mass Spec: *m/z* 537.2 (M+H)⁺.

20

Example 8

Benzofuran-2-carboxylic acid (4-{4-[(2-hydroxycarbamoyl-6-methyl-phenyl)-methyl-sulfamoyl]-phenoxy}-butyl)-amide

25 The product of Example 7 (0.2 g, 0.37 mmol) was converted to the hydroxamic acid using the procedure of Example 4 to provide 0.063 g (31% yield) of a white solid. MP 131-134 °C; ¹H NMR (DMSO-d₆): δ 1.7-1.8 (m, CH₂, CH₂), 1.9 (s, CH₃), 3.20 (s, CH₃), 3.34-3.41 (m, CH₂, CH₂), 7.0-7.1 (d, 1 Ar H), 7.19 (d, 1 Ar H), 7.30-7.78 (m, 9 Ar H), 7.9 (d, 1 Ar H), 8.79 (t, NH), 8.88 (br s, NH), 10.99 (s, OH). Electrospray Mass Spec: 552.2 *m/z* (M+H)⁺.

30

Example 9

2-[(4-{3-[(1H-Indole-2-carbonyl)-amino]-propoxy}-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid

The product of Example 2 (0.27 g, 0.83 mmol) was coupled to N-(3-hydroxypropyl)-1H-indole-2-carboxamide, prepared according to Example 18, (0.20 g, 0.91 mmol) using the procedure of Example 3 to provide 0.4 g (91% yield) of yellow solid powder. MP 199 °C; ¹H NMR (DMSO-d₆): δ 1.9 (s, CH₃), 2.0-2.1 (m, CH₂), 3.20 (s, CH₃), 3.32-3.51 (m, CH₂, CH₂), 6.8-7.2 (m, 8 Ar H), 7.36 (d, 1 Ar H), 7.58 (d, 1 Ar H), 7.78 (d, 1 Ar H), 7.93 (s, 1 NH), 8.52 (s, NH), 12.0 (s, OH).
Electrospray Mass Spec: *m/z* 522.2 (M+H)⁺.

Example 10

1H-Indole-2-carboxylic acid (3-{4-[(2-hydroxycarbamoyl-6-methyl-phenyl)-methyl-sulfamoyl]-phenoxy}-propyl)-amide

The product of Example 9 (0.2 g, 0.38 mmol) was converted to the hydroxamic acid using the procedure of Example 4 to provide 0.112 g (55% yield) of a white solid. MP 144-146 °C; ¹H NMR (DMSO-d₆): δ 1.9 (s, CH₃), 1.35-1.62 (m, CH₂), 3.20 (s, CH₃), 3.46-3.51 (m, CH₂, CH₂), 7.0-7.19 (m, 5 Ar H), 7.28-7.40 (m, 3 Ar H), 7.43-7.55 (m, 2 Ar H), 7.7 (d, 2 Ar H), 8.58 (t, NH), 8.9 (br s, NH), 10.9 (s, NH), 11.7 (s, OH). Electrospray Mass Spec: *m/z* 537.1 (M+H)⁺.

Example 11

2-[(4-{3-[(Benzo[b]thiophene-2-carbonyl)-amino]-ethoxy}-benzenesulfonyl)-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid

The product of Example 2 (0.15 g, 0.846 mmol) was coupled to N-(2-hydroxyethyl)-1-benzothiophene-2-carboxamide, prepared according to Example 19, (0.11 g, 0.51 mmol) using the procedure of Example 3 to provide 0.26 g (80% yield) of yellow solid. MP 250 °C; ¹H NMR (DMSO-d₆): δ 1.9 (s, CH₃), 3.20 (s, CH₃), 3.6 (m, CH₂), 4.1 (m, CH₂), 7.0-7.17 (m, 4 Ar H), 7.34-7.37 (m, 2 Ar H), 7.81-7.95 (m, 6 Ar H), 8.52 (s, NH). Electrospray Mass Spec: *m/z* 525.0 (M+H)⁺.

Example 12

Benzo[b]thiophene-2-carboxylic acid (2-{4-[(2-hydroxycarbamoyl-6-methyl-phenyl)-methyl-sulfamoyl]-phenoxy}-ethyl)-amide

The product of Example 11 (0.2 g, 0.38 mmol) was converted to the hydroxamic acid using the procedure of Example 4 to provide 0.048 g (25% yield) of a white solid. MP 169-171 °C ¹H NMR (DMSO-d₆): δ 1.35-1.62 (m, CH₂), 1.9 (s, CH₃), 3.20 (s, CH₃), 3.46-3.51 (m, CH₂, CH₂), 7.0-7.95 (m, 11 Ar H), 8.0 (s, 1 Ar

H), 8.58 (t, N H), 9.0 (br s, NH), 10.9 (s, OH). Electrospray Mass Spec: m/z 540.2 (M+H)⁺.

Example 13

5 **2-[[[(4-{3-[(1,3-Benzodioxol-5-ylcarbonyl)amino]propoxy}phenyl)sulfonyl](methylamino)-3-methyl benzoic acid**

The product of Example 2 (0.30 g, 0.92 mmol) was coupled to N-(3-hydroxypropyl)-1,3-benzodioxole-5-carboxamide, prepared according to Example 20, (0.205 g, 0.92 mmol) using the procedure of Example 3 to provide 0.23 g (49% yield) of yellow solid. MP 120 °C; ¹H NMR (DMSO-d₆): δ 1.63 (m, CH₂) 1.9 (s, CH₃), 3.20 (s, CH₃), 3.6 (m, CH₂), 4.1 (m, CH₂), 6.07 (s, CH₂), 6.9-7.1 (m, 5 Ar H), 7.3-7.5 (m, 3 Ar H), 7.88-7.94 (m, 2 Ar H), 8.52 (br s, NH). Electrospray Mass Spec: m/z 527.2 (M+H)⁺.

Example 14

15 **N-{3-[4-({2-[(Hydroxyamino)carbonyl]-6-dimethylanilino}sulfonyl)phenoxy]propyl}-1,3-benzodioxole-5-carboxamide**

The product of Example 13 (0.2 g, 0.38 mmol) was converted to the hydroxamic acid using the procedure of Example 4 to provide 0.102 g (50% yield) of a white solid. MP 102-112 °C; ¹H NMR (DMSO-d₆): δ 1.63 (m, CH₂) 1.9 (s, CH₃), 3.20 (s, CH₃), 3.6 (m, CH₂), 4.1 (m, CH₂), 6.08 (s, CH₂), 6.96-6.99 (m, Ar H), 7.02-7.09 (m, 3 Ar H), 7.30-7.45 (, 3 Ar H), 7.52-7.58 (m, 2 Ar H), 7.69-7.72 (d,d, 1 Ar H), 7.82-7.85 (d, 1 Ar H), 8.25 (m, NH), 8.40 (br s, NH), 10.9 (br s, OH). Electrospray Mass Spec: m/z 542.1 (M+H)⁺.

Example 15

25 **2-[[[(4-{4-[(1,3-Benzodioxol-5-ylcarbonyl)amino]butoxy}phenyl)sulfonyl](methylamino)-3-methyl benzoic acid**

The product of Example 2 (0.30 g, 0.92 mmol) was coupled to N-(4-hydroxybutyl)-1,3-benzodioxole-5-carboxamide, prepared according to Example 21, (0.23 g, 0.96 mmol) using the procedure of Example 3 to provide 0.30 g (60% yield) of yellow solid. MP 110 °C; ¹H NMR (DMSO-d₆): δ 1.66-1.80 (m, CH₂, CH₂) 1.89 (s, CH₃), 3.1 (s, CH₃), 3.39-3.45 (m, CH₂), 4.08 (t, CH₂), 6.08 (s, CH₂), 6.9 (d, 1 Ar

H), 7.04-7.08 (m, 2 Ar H), 7.33-7.45 (m, 5 Ar H), 7.53-7.58 (m, 2 Ar H), 8.39 (t, NH), 12.8 (s, OH). Electrospray Mass Spec: m/z 541.2 (M+H)⁺.

Example 16

5 N-{4-[4-({2-[(Hydroxyamino)carbonyl]-6-dimethylanilino}sulfonyl)phenoxy]butyl}-1,3-benzodioxole-5-carboxamide

The product of Example 15 (0.15 g, 0.28 mmol) was converted to the hydroxamic acid using the procedure of Example 4 to provide 0.092 g (40% yield) of a white solid. MP 117-121 °C; ¹H NMR (DMSO-d₆): δ 1.66-1.80 (m, CH₂, CH₂) 1.89 (s, CH₃), 3.1 (s, CH₃), 3.39-3.45 (m, CH₂), 4.08 (t, CH₂), 6.08 (s, CH₂), 6.96 (d, 1
10 Ar H), 7.04-7.08 (d, d 2 Ar H), 7.17-7.19 (d, d 1 Ar H), 7.28-7.38 (m, 3 Ar H), 7.45 (d, d 1 Ar H), 7.68-7.80 (m, 2 Ar H), 7.95 (s, 1 Ar H), 8.32 (t, NH), 8.88 (br s, NH), 11.0 (s, OH). Electrospray Mass Spec: m/z 540.2 (M+H)⁺.

Example 17

N-(4-Hydroxybutyl)-1-benzofuran-2-carboxamide

15 2-Benzofurancarboxylic acid (5.0 g, 30.8 mmol) and 4-amino-1-butanol (3.4 ml, 37 mmol) were dissolved in DMF (45 ml). 1-hydroxybenzotriazole (5.0 g, 37 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (7.7 g, 40 mmol), and diisopropylethylamine (10.7 ml, 61.7 mmol) were added sequentially to the solution and allowed to stir at room temperature overnight. After removing excess
20 solvent in vacuo, the residue was taken up in water and the product was extracted into dichloromethane. The organics were combined, washed with brine, dried over Na₂SO₄, and solvent removed in vacuo to give a solid which was purified by column chromatography (100% ethyl acetate) to give 3.5 g (50% yield) of a white solid. ¹H NMR (DMSO-d₆): δ 1.35-1.62 (m, CH₂, CH₂), 3.29 (q, CH₂), 3.41 (q, CH₂), 4.3 (t, NH), 7.78 (d, 1 Ar H), 7.63 (d, 1 Ar H), 7.51 (s, 1 Ar H), 7.46 (t, 1 Ar H), 7.35 (t, 1
25 Ar H), 8.71 (t, NH) Electrospray Mass Spec: m/z 234.2 (M+H)⁺.

Example 18

N-(3-Hydroxypropyl)-1H-indole-2-carboxamide

30 1H Indole-2-carboxylic acid (5.0 g, 31 mmol) and 3-amino-1-propanol (2.2 ml, 40.3 mmol) were coupled according to the procedure of Example 17 to 5.46 g (80% yield) of an off-white solid. MP 152-156 °C; ¹H NMR (DMSO-d₆): δ 1.6-1.7 (m, CH₂), 3.31-3.37 (q, CH₂), 3.41-3.51 (q, CH₂), 4.52 (t, NH), 7.0-7.19 (m, 3 Ar

H), 7.40 (d, 1 Ar H), 7.58 (d, 1 Ar H), 8.46 (t, NH), 11.9 (s, NH) Electrospray Mass Spec: m/z 217.2 (M+H)⁺.

Example 19

N-(2-Hydroxyethyl)-1-benzothiophene-2-carboxamide

5 2-Benzothiophenecarboxylic acid (3.0 g, 16.8 mmol) and ethanolamine (1.21 ml, 20 mmol) were coupled according to the procedure of Example 17 to 2.7 g (73% yield) of an off-white solid. ¹H NMR (DMSO-d₆): δ 3.3 (m, CH₂), 3.5 (q, CH₂), 4.79 (t, NH), 7.1-7.4 (m, 2 Ar H), 7.90 (m, 1 Ar H), 7.95 (m, 1 Ar H), 8.09 (s, 1 Ar H), 8.89 (t, NH) Electrospray Mass Spec: m/z 222.2 (M+H)⁺.

10

Example 20

N-(3-Hydroxypropyl)-1,3-benzodioxole-5-carboxamide

1,3-Benzodioxole -5-carboxylic acid (2.0 g, 12.0 mmol) and 3-amino-1-propanol (0.8 ml, 15.6 mmol) were coupled according to the procedure of Example 17 to 1.74 g (65% yield) of a white solid. MP 112-113 °C; ¹H NMR (DMSO-d₆): δ 1.65 (m, CH₂), 3.27 (m, CH₂), 3.42 (m, CH₂), 4.45 (t, NH), 6.0 (s, CH₂), 6.98 (d, 1 Ar H), 7.37 (d, 1 Ar H), 7.4 (d-d, 1 Ar H), 8.28 (t, NH) Electrospray Mass Spec: m/z 224.2 (M+H)⁺.

15

Example 21

N-(4-Hydroxybutyl)-1,3-benzodioxole-5-carboxamide

20 1,3-Benzodioxole -5-carboxylic acid (2.0 g, 12.0 mmol) and 4-amino-1-butanol (1.4 ml, 15.6 mmol) were coupled according to the procedure of Example 17 to 2.1 g (75% yield) of a pale yellow solid. MP 95-98 °C; ¹H NMR (DMSO-d₆): δ 1.38-1.65 (m, CH₂, CH₂), 3.31 (q, CH₂), 3.39 (q, CH₂), 4.39 (t, NH), 6.08 (s, CH₂), 6.98 (d, 1 Ar H), 7.37 (d, 1 Ar H), 7.4 (d-d, 1 Ar H), 8.27 (t, NH) Electrospray Mass Spec: m/z 238.2 (M+H)⁺.

25

Example 22

N-(2-Hydroxyethyl) 2-quinolinecarboxamide

To a solution of quinaldic acid (5.0 g, 28.87 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.5 g, 28.87 mmol), and 1-hydroxybenzotriazole (5.1 g, 37.49 mmol) in DMF (60 mL) at 0 °C was added ethanolamine (1.74 mL, 28.87 mmol) and 4-methylmorpholine (4.76 mL, 43.31 mmol). The reaction was stirred at 0 °C for an additional 10 minutes and then

30

warmed to room temperature and stirred for 2 hours. The reaction mixture was then diluted with ethyl acetate, washed 3 times with H₂O, once with NaHCO₃ (sat), once with brine, dried over MgSO₄, and concentrated in vacuo to provide 1.5 g (24% yield) of a pale yellow solid. Electrospray Mass Spec: *m/z* 216.8 (M+H)⁺.

5

Example 23

N-(3-Hydroxypropyl)-1-benzofuran-2-carboxamide

2-Benzofurancarboxylic acid (5.0 g, 30.8 mmol) and 3-amino-1-propanol (2.83 ml, 37 mmol) were coupled according to the procedure of example 22 to provide 1.39 g (17.2 % yield) of the desired product as a yellow solid. Electrospray Mass Spec: *m/z* 219.8 (M+H)⁺.

10

Example 24

N-(3-Hydroxypropyl)-1-benzothiophene-2-carboxamide

2-Benzothiophenecarboxylic acid (5.0 g, 28.05 mmol) and 3-amino-1-propanol (2.57 ml, 33.66 mmol) were coupled according to the procedure of Example 22 to provide 3.45 g (52.3 % yield) of the desired product as an orange solid. Electrospray Mass Spec: *m/z* 235.9 (M+H)⁺.

15

Example 25

N-(2-Hydroxypropyl)-1-benzofuran-2-carboxamide

2-Benzofurancarboxylic acid (1.0 g, 6.16 mmol) and ethanolamine (0.37 ml, 6.16 mmol) were coupled according to the procedure of Example 22 to provide 0.55 g (43 % yield) of the desired product as a yellow solid. MP 90-91 °C. Electrospray Mass Spec: *m/z* 205.8 (M+H)⁺.

20

Example 26

2-[[[(4-{3-[(1-Benzothiophene-2-

ylcarbonyl)amino]propoxy}phenyl)sulfonyl](methylamino)-3-methyl benzoic acid

25

The product of Example 2 (0.5 g, 1.58 mmol) was coupled to N-(3-hydroxypropyl)-1-benzothiophene-2-carboxamide (1.26 g, 5.37 mmol) using the procedure of Example 3 to provide 0.16 g (19% yield) of an off white solid.

30

Electrospray Mass Spec: *m/z* 539.3 (M+H)⁺.

Example 27

N-{3-[4-({2-[(Hydroxyamino)carbonyl]-6-dimethylanilino}-sulfonyl)phenoxy]propyl}-1-benzothiophene-2-carboxamide

The product of Example 26 (0.16 g, 0.30 mmol) was converted to the hydroxamic acid using the procedure of Example 4 to provide 0.1 g (60% yield) as a pink foam. MP 100-105 °C. Electrospray Mass Spec: m/z 554.0 (M+H)⁺.

Example 28

2-(4-Fluoro-benzenesulfonylamino)-3,5-dimethyl-benzoic acid methyl ester

To a solution of 2.00g (0.011 mmol) of methyl 3,5-dimethylantranilic acid in 10.0mL of pyridine was added 2.17 (0.011 mmol) of 4-fluorobenzenesulfonyl chloride. The reaction mixture was stirred for 24h at room temperature and then diluted with chloroform and washed with 5% HCl solution and water. The organic layer was then dried over MgSO₄, filtered and concentrated in vacuo. The residue was triturated with ether-hexanes and the resulting solid was filtered and dried to provide 3.09 g (82%) of the desired product as a white solid. Electrospray Mass Spec: m/z 338.3 (M+H)⁺.

Example 29

2-[Benzyl-(4-fluoro-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid methyl ester

To a solution of 1.00g (2.86 mmol) of the product of Example 28 in 10mL of DMF was added 0.14 g (3.57mmol) of 60% sodium hydride. The resulting mixture was stirred for 30 min at room temperature and then 0.42 mL (3.57 mmol) of benzyl bromide was added. This reaction mixture was stirred overnight at room temperature, poured into water and then extracted with ether. The combined organics were washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo to provide a white solid which was recrystallized from ethyl acetate (EtOAc)/Hexanes to provide 1.084g (85%) of the desired product as a white solid. Electrospray Mass Spec: m/z 428.3 (M+H)⁺.

Example 30

2-[[4-{2-[(Benzofuran-2-carbonyl)-amino]ethoxy}benzenesulfonyl]benzylamino]-3,5-dimethyl-benzoic acid

Sodium hydride (0.240 g, 5.99 mmol, 60% dispersion in mineral oil) was added to DMF (8 ml) and cooled to 0 °C. A solution of N-(2-hydroxypropyl)-1-benzofuran-2-carboxamide (0.6 g, 2.92 mmol) in DMF (1.5 ml) was added and allowed to stir for 10 min at 0 °C and then for 15 min at rt. The product of Example 29 (0.383 g, 0.87 mmol) was then added in one portion and the reaction was allowed

to stir overnight. The reaction was then quenched with water, extracted with EtOAc, washed with water, brine, dried over MgSO_4 , and concentrated in vacuo to provide an oil which was chromatographed using hexane to 2/1 hexane/EtOAc as eluant to provide the product as a mixture of esters which was used directly in the next

5 reaction. The mixture of esters (233 mg) was dissolved in THF:MeOH:H₂O (1.2mL:0.7 mL:1.2 mL) and LiOH (13.7 mg, 0.32 mmol) was added. The reaction was heated at reflux overnight. The reaction was cooled to rt, quenched with 6M HCl and extracted with CH_2Cl_2 . The organics were washed with brine, dried over Na_2SO_4 , concentrated in vacuo to provide an oil which was chromatographed using

10 hexane to 9/1 CH_2Cl_2 /MeOH as eluant to provide 80 mg (44% yield) of the product acid. Electrospray Mass Spec: m/z 597.2 (M-H)-.

Example 31

Benzofuran-2-carboxylic acid (2-{4-[benzyl-(2-hydroxycarbamoyl-4,6-dimethyl-phenyl)-sulfamoyl]-phenoxy}-ethyl)-amide

15 DMF (0.0021 mL, 0.26mmol) was added to oxalyl chloride (0.13mL, 0.267 mmol, 2M in CH_2Cl_2) at 0 °C. This mixture was allowed to warm to rt and stir for 45 min. To this suspension was added a solution of the product from Example 30 (80 mg, 0.13 mmol) in DMF (1 mL). The solution of the acid chloride was then stirred for 4 hours.

20 In a separate flask, 0.27mL (1.95 mmol) of triethylamine was added to 0 °C mixture of 0.09 g (1.3 mmol) of hydroxylamine hydrochloride in 1.49 mL of THF and 0.43 mL of water. After this mixture had stirred for 15min at 0 °C, the acid chloride solution was added to it in one portion and the resulting solution was allowed to warm to room temperature with stirring overnight. The reaction mixture was then

25 acidified to pH3 with 10% HCl and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated in vacuo. The crude residue was chromatographed using 95/5 CH_2Cl_2 /MeOH as eluant to provide 0.020g (25%) of the desired hydroxamic acid as a white solid. Electrospray Mass Spec: m/z 612.2 (M-H)-.

Pharmacology

Procedures for Measuring MMP-1, MMP-9, and MMP-13 Inhibition

5

These assays are based on the cleavage of a thiopeptide substrates such as Ac-Pro-Leu-Gly(2-mercapto-4-methyl-pentanoyl)-Leu-Gly-OEt by the matrix metalloproteinases MMP-1, MMP-13 (collagenases) or MMP-9 (gelatinase), which results in the release of a substrate product that reacts colorimetrically with DTNB (5,5'-dithiobis(2-nitro-benzoic acid)). The enzyme activity is measured by the rate of the color increase. The thiopeptide substrate is made up fresh as a 20 mM stock in 100% DMSO and the DTNB is dissolved in 100% DMSO as a 100 mM stock and stored in the dark at room temperature. Both the substrate and DTNB are diluted together to 1 mM with substrate buffer (50 mM HEPES pH 7.5, 5 mM CaCl_2) before use. The stock of enzyme is diluted with assay buffer (50 mM HEPES, pH 7.5, 5 mM CaCl_2 , 0.02% Brij) to the desired final concentration. The assay buffer, enzyme, vehicle or inhibitor, and DTNB/substrate are added in this order to a 96 well plate (total reaction volume of 200 μl) and the increase in color is monitored spectrophotometrically for 5 minutes at 405 nm on a plate reader and the increase in color over time is plotted as a linear line.

Alternatively, a fluorescent peptide substrate is used. In this assay, the peptide substrate contains a fluorescent group and a quenching group. Upon cleavage of the substrate by an MMP, the fluorescence that is generated is quantitated on the fluorescence plate reader. The assay is run in HCBC assay buffer (50mM HEPES, pH 7.0, 5 mM Ca^{+2} , 0.02% Brij, 0.5% Cysteine), with human recombinant MMP-1, MMP-9, or MMP-13. The substrate is dissolved in methanol and stored frozen in 1 mM aliquots. For the assay, substrate and enzymes are diluted in HCBC buffer to the desired concentrations. Compounds are added to the 96 well plate containing enzyme and the reaction is started by the addition of substrate. The reaction is read (excitation 340 nm, emission 444 nm) for 10 min. and the increase in fluorescence over time is plotted as a linear line.

For either the thiopeptide or fluorescent peptide assays, the slope of the line is calculated and represents the reaction rate. The linearity of the reaction rate is confirmed ($r^2 > 0.85$). The mean ($x \pm \text{sem}$) of the control rate is calculated and compared for statistical significance ($p < 0.05$) with drug-treated rates using Dunnett's multiple comparison test. Dose-response relationships can be generated using

multiple doses of drug and IC₅₀ values with 95% CI are estimated using linear regression.

Procedure for Measuring TACE Inhibition

5 Using 96-well black microtiter plates, each well receives a solution composed of 10 μ L tumor necrosis factor- α converting enzyme (TACE; Immunex, final concentration 1 μ g/mL), 70 μ L Tris buffer, pH 7.4 containing 10% glycerol (final concentration 10 mM), and 10 μ L of test compound solution in DMSO (final
10 concentration 1 μ M, DMSO concentration <1%) and incubated for 10 minutes at room temperature. The reaction is initiated by addition of a fluorescent peptidyl substrate (final concentration 100 μ M) to each well and then shaking on a shaker for 5 sec.

The reaction is read (excitation 340 nm, emission 420 nm) for 10 min. and the increase in fluorescence over time is plotted as a linear line. The slope of the line is
15 calculated and represents the reaction rate.

The linearity of the reaction rate is confirmed ($r^2 > 0.85$). The mean ($x \pm \text{sem}$) of the control rate is calculated and compared for statistical significance ($p < 0.05$) with drug-treated rates using Dunnett's multiple comparison test. Dose-response relationships can be generate using multiple doses of drug and IC₅₀ values with 95%
20 CI are estimated using linear regression.

Results of the above in-vitro matrix metalloproteinase inhibition and TACE inhibition pharmacological assays are given in Table I below.

Biological Data:

Exempl	MMP-1 ^a	MMP-9 ^a	MMP-13 ^a	TACE ^b
4	4244	337	73	19.9
6	5450	510	4.9	21.3
8	5122	84	467	43.6
10	5642	305	178	35.7
12	>10 μ M	914	595	15.2
14	1481	63.6	110	42.1
16	999	55.7	83.5	27.4
27	30 μ M	1390	43	22.0
31	10 μ M	945	17.1	18.9

a) IC₅₀ (nM)5 b) % inhibition @1 μ M

Compounds of this invention are shown to inhibit the enzymes MMP-1, MMP-9, MMP-13, and TACE and are therefore useful in the treatment of conditions resulting from overexpression or excess activation of MMPs and TACE. Such

10 diseases are, for example, atherosclerosis, atherosclerotic plaque formation, reduction of coronary thrombosis from atherosclerotic plaque rupture, restenosis, MMP-mediated osteopenias, inflammatory diseases of the central nervous system, skin aging, angiogenesis, tumor metastasis, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound healing, bone disease,

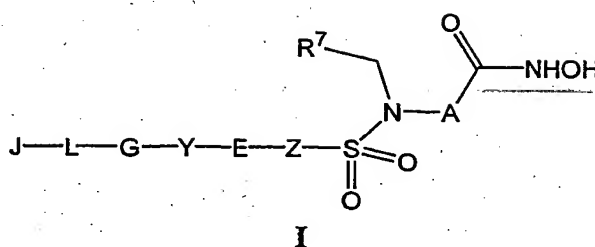
15 proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease, and periodontal disease. Compounds of the present invention are also believed to be useful for the treatment of age related macular

20 degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neovascularization or corneal graft rejection. In addition, compounds of the present invention are believed to be useful for the treatment of graft rejection, cachexia, anorexia, inflammation, fever, insulin resistance, septic shock,

25 congestive heart failure, inflammatory disease of the central nervous system, or HIV infection.

5 What is claimed is:

1. A compound of formula I



10

where the hydroxamic acid moiety and the sulfonamido moiety are bonded to adjacent carbons of group A wherein:

A is aryl, heteroaryl or heteroaryl fused to a phenyl ring;

Z is aryl, heteroaryl, or heteroaryl fused to a phenyl;

15 E and G are independently CH₂, NR⁵, or O, or S or a bond:

Y is cycloalkyl, cycloheteroalkyl, -C₁-C₅-perfluoroalkyl, alkyl, alkenyl, alkynyl, heteroalkyl, alkylaryl, or heteroaryl;

J is aryl, heteroaryl, heteroaryl fused to a phenyl, cycloalkyl, cycloheteroalkyl, -C₁-C₅-perfluoroalkyl, alkyl, alkenyl, or alkynyl;

20 R⁵ and R⁶ are independently H, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, -C₁-C₄-perfluoroalkyl, alkyl, alkenyl, or alkynyl;

R⁷ is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl or 3-6 membered cycloheteroalkyl;

25 or

R⁷CH₂-N-A- can form a non-aromatic 1,2-benzo-fused 7-10 membered heterocyclic ring optionally containing an additional heteroatom selected from O, S and N wherein said heterocyclic ring may be optionally fused to another benzene ring;

30 L is -C(O)-, S(O)_y, -NR⁵C(O)NR⁶-, -NR⁵C(O)O-, -OC(O)NR⁵-, -SC(O)-, -C(O)S-, -NR⁵C(O)-, -C(O)NR⁵-, -SC(O)NR⁵-, -NR⁵C(O)S-, -OC(O)O-;

y is 1 or 2;

and the pharmaceutically acceptable salts thereof and the optical isomers and diastereomers thereof.

- 5 2. The compound according to Claim 1 wherein A is aryl, heteroaryl or heteroaryl fused to a phenyl ring optionally substituted by R¹, R², R³ and R⁴; Z is aryl, heteroaryl, or heteroaryl fused to a phenyl, optionally substituted by R¹⁰, R¹¹, R¹² and R¹³;

- 10 R¹, R², R³, R⁴, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, R³⁰ and R³¹ are independently -H, -COR⁵, -F, -Br, -Cl, -I, C(O)NR⁵OR⁶, -CN, -OR⁵, -C₁-C₄-perfluoroalkyl, -S(O)_xR⁵, -OPO(OR⁵)OR⁶, -PO(OR⁶)R⁵, -OC(O)NR⁵R⁶, -COOR⁵, -CONR⁵R⁶, -SO₃H, -NR⁵R⁶, -NR⁵COR⁶, -NR⁵COOR⁶, -SO₂NR⁵R⁶, -NO₂, -N(R⁵)SO₂R⁶, -NR⁵CONR⁵R⁶NR⁵C(=NR⁶)NR⁵R⁶, 3-6 membered cycloheteroalkyl, aryl, 15 heteroaryl, biphenyl, -SO₂NHCOR¹⁸, -CONHSO₂R¹⁸, -tetrazol-5-yl, -SO₂NHCN, -SO₂NHCONR⁵R⁶ or straight chain or branched -C₁-C₆ alkyl, -C₂-C₆-alkenyl, or -C₂-C₆-alkynyl, or -C₃-C₆-cycloalkyl, each optionally substituted with -COR⁵, -CN, -C₂-C₆ alkenyl, -C₂-C₆ alkynyl, -OR⁵, -C₁-C₄-perfluoroalkyl, -S(O)_xR⁵, -OC(O)NR⁵R⁶, -COOR⁵, -CONR⁵R⁶, -SO₃H, -NR⁵R⁶, -NR⁵COR⁶, -NR⁵COOR⁶, -SO₂NR⁵R⁶, -NO₂, -N(R⁵)SO₂R⁶, -NR⁵CONR⁵R⁶, -C₃-C₆cycloalkyl, 3-6 membered 20 cycloheteroalkyl, aryl, heteroaryl, biphenyl, -SO₂NHCOR¹⁸, -CONHSO₂R¹⁸; -PO(OR⁵)OR⁶, -PO(OR⁶)R⁵, -tetrazol-5-yl, C(O)NR⁵OR⁶, -NR⁵C(=NR⁶)NR⁵R⁶, -SO₂NHCONR⁵R⁶ or -SO₂NHCN; or

- 25 when any of R¹ and R² or R¹⁰ and R¹¹ or R¹⁴ and R¹⁵ are on adjacent carbons of A or J or Z respectively, then each pair of R¹ and R² or R¹⁰ and R¹¹ or R¹⁴ and R¹⁵ together with the carbons to which they are attached can form a 5 to 7 membered saturated or unsaturated heterocyclic ring, a 5-6 membered heteroaryl ring, or a 5 to 7 membered saturated or unsaturated carbocyclic ring;

x is 0-2;

- 30 E and G are independently CH₂, NR⁵, or O, or S or a bond:

Y is -C₃-C₆-cycloalkyl, -C₃-C₆-cycloheteroalkyl, -C₁-C₅-perfluoroalkyl, straight chain or branched -C₁-C₆ alkyl, straight or branched chain -C₂-C₆-alkenyl, or

straight or branched chain C₂-C₆-alkynyl or heteroalkyl, alkylaryl, heteroaryl optionally substituted with R²⁰, R²¹, R²², and R²³;

J is aryl, heteroaryl, or heteroaryl fused to a phenyl; optionally substituted with R¹⁴, R¹⁵, R¹⁶, and R¹⁷ or -C₃-C₆-cycloalkyl, -C₃-C₆-cycloheteroalkyl, -C₁-C₅-perfluoroalkyl, straight chain or branched -C₁-C₆ alkyl, straight or branched chain -C₂-C₆-alkenyl, or straight or branched chain C₂-C₆-alkynyl;

R⁵ and R⁶ are independently H, aryl, heteroaryl, -C₃-C₆-cycloalkyl, -C₃-C₆-cycloheteroalkyl, -C₁-C₄-perfluoroalkyl, or straight chain or branched -C₁-C₆ alkyl, -C₂-C₆-alkenyl, or -C₂-C₆-alkynyl, each optionally substituted with -OH, -COR⁸, -CN, -C(O)NR⁸OR⁹, -C₂-C₆-alkenyl, -C₂-C₆-alkynyl, -OR⁸, -C₁-C₄-perfluoroalkyl, -S(O)_xR⁸, -OPO(OR⁸)OR⁹, -PO(OR⁸)R⁹, -OC(O)NR⁸R⁹, -COOR⁸, -CONR⁸R⁹, -SO₃H, -NR⁸R⁹, -NCOR⁸R⁹, -NR⁸COOR⁹, -SO₂NR⁸R⁹, -NO₂, -N(R⁸)SO₂R⁹, -NR⁸CONR⁸R⁹, -C₃-C₆ cycloalkyl, 3-6 membered cycloheteroalkyl, aryl, heteroaryl, -SO₂NHCOR¹⁹, -CONHSO₂R¹⁹, -tetrazol-5-yl, NR⁸C(=NR⁹)NR⁸R⁹, -SO₂NHCONR⁸R⁹, or -SO₂NHCN;

R⁷ is hydrogen, straight chain or branched -C₁-C₆-alkyl, -C₂-C₆-alkenyl, or -C₂-C₆-alkynyl each optionally substituted with -OH, -COR⁵, -CN, -C₂-C₆-alkenyl, -C₂-C₆-alkynyl, -OR⁵, -C₁-C₄-perfluoroalkyl, -S(O)_xR⁵, OPO(OR⁵)OR⁶, -PO(OR⁵)R⁶, -OC(O)NR⁵R⁶, -COOR⁵, -CONR⁵R⁶, -SO₃H, -NR⁵R⁶, -NR⁵COR⁶, -NR⁵COOR⁶, -SO₂NR⁵R⁶, -NO₂, -N(R⁵)SO₂R⁶, -NR⁵CONR⁵R⁶, -C₃-C₆ cycloalkyl, -C₃-C₆-cycloheteroalkyl, -aryl, heteroaryl, -SO₂NHCOR³², -CONHSO₂R³², -tetrazol-5-yl, -NR⁵C(=NR⁶)NR⁵R⁶, -C(O)NR⁵OR⁶, -SO₂NHCONR⁵R⁶ or -SO₂NHCN;

or R⁷ is phenyl or naphthyl, optionally substituted by R²⁴, R²⁵, R²⁶ and R²⁷ or a 5 to 6 membered heteroaryl group optionally substituted by R²⁸, R²⁹, R³⁰ and R³¹; or

R⁷ is C₃-C₆ cycloalkyl or 3-6 membered cycloheteroalkyl; or

R⁷CH₂-N-A- can form a non-aromatic 1,2-benzo-fused 7-10 membered heterocyclic ring optionally containing an additional heteroatom selected from O, S and N wherein said heterocyclic ring may be optionally fused to another benzene ring;

R⁸ and R⁹ are independently H, aryl or heteroaryl, -C₃-C₇ cycloalkyl or 3 to 6 membered cycloheteroalkyl, -C₁-C₄-

perfluoroalkyl, straight chain or branched -C₁-C₆-alkyl, -C₂-C₆-alkenyl, or -C₂-C₆-alkynyl, each optionally substituted with hydroxy, alkoxy, aryloxy, -C₁-C₄-perfluoroalkyl, amino, mono- and di-C₁-C₆-alkylamino, carboxylic acid, carboalkoxy and carboaryloxy, nitro, cyano, carboxamido primary, mono- and di-C₁-C₆-alkylcarbamoyl;

R¹⁸ and R³² are independently aryl, heteroaryl, -C₃-C₆-cycloalkyl, -C₃-C₆-cycloheteroalkyl, -C₁-C₄-perfluoroalkyl, or straight chain or branched -C₁-C₆ alkyl, -C₂-C₆-alkenyl, or -C₂-C₆-alkynyl, each optionally substituted with -OH, -COR⁸, -CN, -C(O)NR⁸OR⁹, -C₂-C₆-alkenyl, -C₂-C₆-alkynyl, -OR⁸, -C₁-C₄-perfluoroalkyl, -S(O)_xR⁸, -OPO(OR⁸)OR⁹, -PO(OR⁸)R⁹, -OC(O)NR⁸R⁹, -COOR⁸, -CONR⁸R⁹, -SO₃H, -NR⁸R⁹, -NCOR⁸R⁹, -NR⁸COOR⁹, -SO₂NR⁸R⁹, -NO₂, -N(R⁸)SO₂R⁹, -NR⁸CONR⁸R⁹, -C₃-C₆ cycloalkyl, 3-6 membered cycloheteroalkyl, aryl, heteroaryl, -SO₂NHCOR¹⁹, -CONHSO₂R¹⁹, -tetrazol-5-yl, NR⁸C(=NR⁹)NR⁸R⁹, -SO₂NHCONR⁸R⁹, or -SO₂NHCN;

R¹⁹ is aryl or heteroaryl, -C₃-C₇cycloalkyl or 3 to 6 membered cycloheteroalkyl, -C₁-C₄-perfluoroalkyl, straight chain or branched -C₁-C₆-alkyl, -C₂-C₆-alkenyl, or -C₂-C₆-alkynyl, each optionally substituted with hydroxy, alkoxy, aryloxy, -C₁-C₄-perfluoroalkyl, amino, mono- and di-C₁-C₆-alkylamino, carboxylic acid, carboalkoxy and carboaryloxy, nitro, cyano, carboxamido primary, mono- and di-C₁-C₆-alkylcarbamoyl;

L is -C(O)-, S(O)_y, -NR⁵C(O)NR⁶-, -NR⁵C(O)O-, -OC(O)NR⁵-, -SC(O)-, -C(O)S-, -NR⁵C(O)-, -C(O)NR⁵-, -SC(O)NR⁵-, -NR⁵C(O)S-, -OC(O)O-;

y is 1 or 2;

and the pharmaceutically acceptable salts thereof and the optical isomers and diastereomers thereof.

3. A compound according to claim 1 or 2 wherein E and G are independently selected from NH, O and S.

4. A compound according to any one of Claims 1 to 3 wherein J is aryl or heteroaryl fused to a phenyl.

5. A compound according to Claim 4 wherein J is quinolyl, benzothienyl, benzofuranyl, benzodioxolyl or indolyl optionally substituted by one or more of R¹⁴, R¹⁵, R¹⁶ and R¹⁷.
- 5 6. A compound according to Claim 4 wherein J is selected from benzofuranyl, benzothienyl, quinolyl, benzodioxolyl or indolyl.
7. A compound according to Claim 4 wherein J is selected from quinol-2-yl, benzo[b]thiophen-2-yl, benzofuran-2-yl, indol-2-yl or 1,3-benzodioxol-2-yl.
- 10 8. A compound according to any one of Claims 1 to 7 wherein A is phenyl optionally substituted by H or straight or branched chain C₁-C₆ alkyl.
9. A compound according to any one of Claims 1 to 8 wherein Z is phenyl.
- 15 10. A compound according to any one of Claims 1 to 9 wherein R⁷ is H, straight or branched chain C₁-C₆ alkyl or phenyl.
11. A compound according to any one of Claims 1 to 10 wherein L is -CO-.
- 20 12. A compound of formula (I) which is selected from the following:
Quinoline-2-carboxylic acid (2-{4-[(2-hydroxycarbamoyl-6-methyl-phenyl)-methyl-sulfamoyl]-phenoxy}-ethyl)-amide;
Benzofuran-2-carboxylic acid (3-{4-[(2-hydroxycarbamoyl-6-methyl-phenyl)-methyl-sulfamoyl]-phenoxy}-propyl)-amide;
- 25 Benzofuran-2-carboxylic acid (4-{4-[(2-hydroxycarbamoyl-6-methyl-phenyl)-methyl-sulfamoyl]-phenoxy}-butyl)-amide;
1H-Indole-2-carboxylic acid (3-{4-[(2-hydroxycarbamoyl-6-methyl-phenyl)-methyl-sulfamoyl]-phenoxy}-propyl)-amide;
- 30 Benzo[b]thiophene-2-carboxylic acid (2-{4-[(2-hydroxycarbamoyl-6-methyl-phenyl)-methyl-sulfamoyl]-phenoxy}-ethyl)-amide;
N-{3-[4-({2-[(Hydroxyamino)carbonyl]-6-dimethylanilino}sulfonyl)-phenoxy]propyl}-1,3-benzodioxole-5-carboxamide;
- 35 N-{4-[4-({2-[(Hydroxyamino)carbonyl]-6-dimethylanilino}sulfonyl)-phenoxy]butyl}-1,3-benzodioxole-5-carboxamide;

N-{3-[4-({2-[(Hydroxyamino)carbonyl]-6-dimethylanilino}-sulfonyl)-phenoxy]propyl}-1-benzothiophene-2-carboxamide; and

Benzofuran-2-carboxylic acid (2-{4-[benzyl-(2-hydroxycarbamoyl)-4,6-dimethyl-phenyl]-sulfamoyl]-phenoxy}-ethyl)-amide.

5

13. A method of treating a pathological condition or disorder mediated by matrix metalloproteinases in mammals which comprises administration to a mammal in need thereof a therapeutically effective amount of a matrix metalloproteinase inhibiting compound according to any one of claims 1-12.

10

14. A method of treating a patient suffering from a condition selected from atherosclerosis, atherosclerotic plaque formation, reduction of coronary thrombosis from atherosclerotic plaque rupture, restenosis, MMP-mediated osteopenias, inflammatory diseases of the central nervous system, skin aging, angiogenesis, tumor metastasis, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound healing, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease, or periodontal disease comprising administering a therapeutically effective amount of a compound defined in any one of claims 1-12.

20

15. A method of treating a patient suffering from a condition selected from age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neovascularization or corneal graft rejection comprising administering a therapeutically effective amount of a compound defined in any one of claims 1-12.

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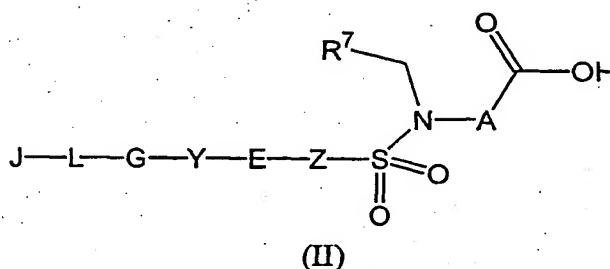
16. A method of treating a patient suffering from a condition selected from rheumatoid arthritis, graft rejection, cachexia, anorexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, or HIV infection comprising administering a therapeutically effective amount of a compound as defined in any one of claims 1-12.

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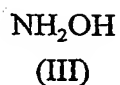
17. A pharmaceutical composition comprising a pharmaceutical carrier and a
therapeutically effective amount of a matrix metalloproteinase inhibiting compound
5 defined in any one of claims 1-12.

18. A process for preparing a compound of formula (I) as claimed in claim 1 which
10 comprises one of the following:

a) reacting a compound of formula II:
15



wherein J, L, G, Y, E, Z, A and R⁷ are defined in claim 1 or a reactive derivative
20 thereof, with a compound of formula III:

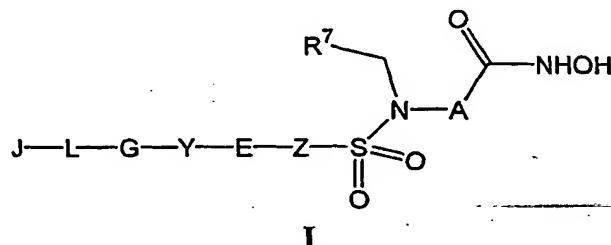


25 to give a corresponding compound of formula I;

b) resolving a mixture (e.g. racemate) of optically active isomers of a compound
of formula I to isolate one enantiomer or diastereomer substantially free of the other
enantiomer or diastereomers;
30

c) acidifying a basic compound of formula I with a pharmaceutically acceptable acid to give a pharmaceutically acceptable salt.

5 19. A process for the preparation of compound of formula I



where the hydroxamic acid moiety and the sulfonamido moiety are bonded to
10 adjacent carbons of group A wherein:

A is aryl, heteroaryl or heteroaryl fused to a phenyl ring;

Z is aryl, heteroaryl, or heteroaryl fused to a phenyl;

E and G are independently CH₂, NR⁵, or O, or S or a bond:

Y is cycloalkyl, cycloheteroalkyl, -C₁-C₅-perfluoroalkyl, alkyl, alkenyl,
15 alkynyl, heteroalkyl, alkylaryl, or heteroaryl;

J is aryl, heteroaryl, heteroaryl fused to a phenyl, cycloalkyl, cycloheteroalkyl,
-C₁-C₅-perfluoroalkyl, alkyl, alkenyl, or alkynyl;

R⁵ and R⁶ are independently H, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl,
-C₁-C₄-perfluoroalkyl, alkyl, alkenyl, or alkynyl;

20 R⁷ is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl or 3-6 membered
cycloheteroalkyl;

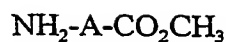
or

R⁷CH₂-N-A- can form a non-aromatic 1,2-benzo-fused 7-10 membered
25 heterocyclic ring optionally containing an additional heteroatom selected from O, S
and N wherein said heterocyclic ring may be optionally fused to another benzene
ring;

L is -C(O)-, S(O)_y, -NR⁵C(O)NR⁶-, -NR⁵C(O)O-, -OC(O)NR⁵-, -SC(O)-, -
C(O)S-, -NR⁵C(O)-, -C(O)NR⁵-, -SC(O)NR⁵-, -NR⁵C(O)S-, -OC(O)O-;

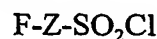
30 y is 1 or 2;

and the pharmaceutically acceptable salts thereof and the optical isomers and
diastereomers thereof; which process comprises reacting

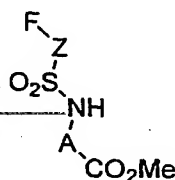


wherein A is as previously defined with

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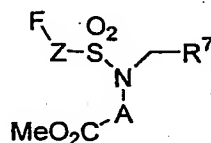


wherein Z is as previously defined to form a first intermediate



alkylating said first intermediate to form a second intermediate

10

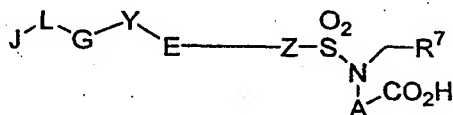


wherein R⁷ is as previously defined;

said second intermediate being a) hydrolyzed to form the carboxylic acid and then subjected to nucleophilic displacement or b) treated directly with a suitable

15

nucleophile and then hydrolyzed to the carboxylic acid to form a third intermediate



wherein J, L, G, Y, and E are as previously defined; and

converting said third intermediate to the corresponding hydroxamic acid to form the compound of formula I.

20

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 01/05349

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D215/48 C07D307/85 C07D209/42 C07D333/70 C07D317/68
A61K31/47 A61K31/34 A61K31/40 A61K31/38 A61K31/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 16514 A (AMERICAN CYANAMIDE CO) 23 April 1998 (1998-04-23) claims	1,13-17
A	WO 98 16503 A (AMERICAN CYANAMID CO) 23 April 1998 (1998-04-23) claims	1,13-17
P,X	WO 00 44710 A (AMERICAN CYANAMID CO) 3 August 2000 (2000-08-03) schemes 1-2; examples 28, 30; page 66, lines 16-37	1,2,9, 10,13-19

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

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- *E* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

31 July 2001

Date of mailing of the international search report

06/08/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Van Amsterdam, L

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/05349

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9816514 A	23-04-1998	AU 4980697 A ZA 9709235 A	11-05-1998 15-04-1999
WO 9816503 A	23-04-1998	AU 731737 B AU 5145898 A BR 9712525 A EP 0938471 A HU 0000641 A TW 410220 B ZA 9709233 A	05-04-2001 11-05-1998 19-10-1999 01-09-1999 28-10-2000 01-11-2000 15-04-1999
WO 0044710 A	03-08-2000	AU 3474400 A	18-08-2000

Application #: 10/751,600
 Filing Date: 01/05/2004
 Inventor: SCHUDOK, et al.
 Docket number: DEAV2003/0001 US NP